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REARRANGEMENT STUDIES AND NOVEL REACTIONS OF ORGANOCADMIUM REAGENTS

JAMES GERARD SHELNUT

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REARRANGEMENT STUDIES AND NOVEL REACTIONS OF ORGANOCADMIUM REAGENTS

by

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This thesis is dedicated to the only real woman, Doris,

and to Superkid, Adam.

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PART I

AN INVESTIGATION INTO AN AROMATIC ORGANOCADMIUM REARRANGEMENT

ABSTRACT

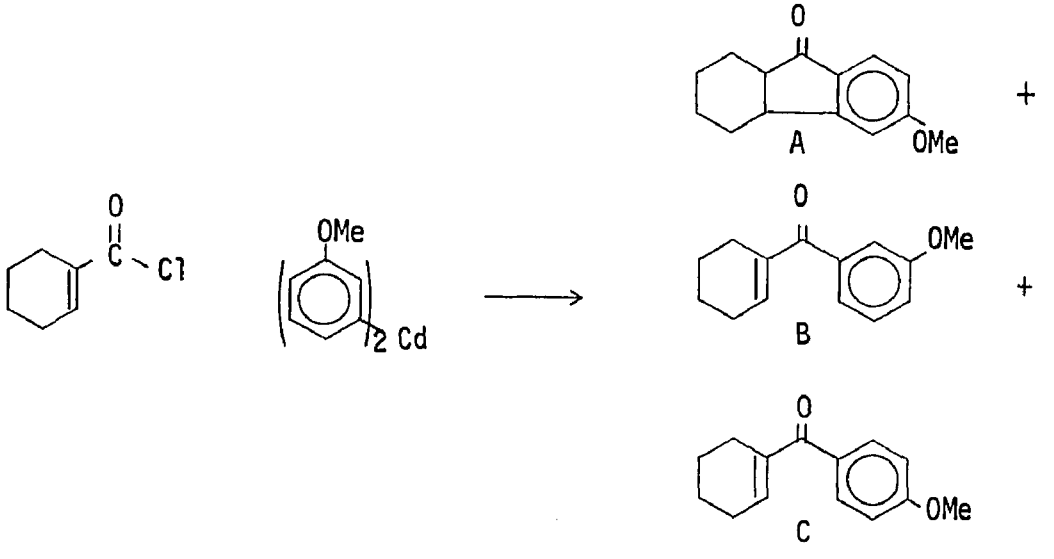
The meta substituted phenyl cadmium derivatives containing trifluoromethyl, fluoro, methyl, methylthio and methoxy were allowed to react with acetyl chloride. Only the methylthio and methoxy compounds gave rearrangement products. The m-dianisylcadmium reagent was allowed to react with acetyl bromide, acetic anhydride and diacetyl sulfide. The acid halides led to more rearrangement than acetic anhydride; with diacetyl sulfide no rearranged product was detected. m-Anisylcadmium chloride, bromide and iodide were allowed to react with acetyl chloride and acetyl bromide, but no difference in the amounts of rearranged product was observed. When the m-dianisyl-cadmium-acetyl chloride adduct was hydrolyzed with DCl/D_2O, no deuterium was incorporated into the ring (nmr). When the 1-methoxy-2,4,6-trideutero-3-phenylcadmium-acetyl chloride adduct was hydrolyzed with acid, some protonation of the ring was noted (nmr, ms). On the basis of control experiments it is believed that exchange of protons had taken place, rather than hydrolysis of the cadmium carbon bond.

Bromine and phenyl cyanate were allowed to react with the m-dianisyl cadmium reagent. It was found that the former gave largely rearranged product (75%), while the latter gave only a small amount (5%) of p-anisonitrile.

INTRODUCTION

In 1957, Klemm and coworkers (1) noted that the reaction between meta-methoxybenzoyl chloride and meta-dianisyl cadmium gave a product whose 2,4-dinitrophenylhydrazone was not identical to that of 3,3'-dimethoxybenzophenone, the expected product. Infrared comparison of the ketonic products with that of standard 3,3'- and 3,4'-dimethoxybenzophenones indicated that the product was made up of a mixture of the "normal" (3,3' isomer) and "rearranged" (3,4' isomer) benzophenones in a ratio of 35:65.

Concurrently, Dauben and Collette (2), investigating the reaction of cyclohexenyl-1-carbonyl chloride with meta-dianisyl cadmium, found the product to contain a mixture of 2-methoxy-4b,5,6,7,8,8a-hexahydrofluorenone (A), and 3- and 4-methoxy-3',4',5',6'-tetrahydrobenzophenone (B,C). By ultraviolet and infrared analyses, the composition was found to be 40% A, 10% B and 50% C (Equation 1).



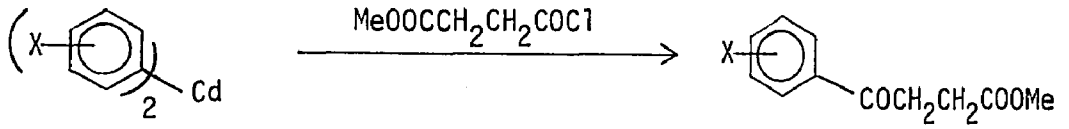
Equation 1

These workers then undertook a study of the scope of this "rearrangement." In the reaction of the isomeric dianisyl cadmium reagents with acetyl chloride, only the meta-isomer gave significant rearranged product (Equation 2).

X=o-MeO-	X=2-MeO- 96%, 4-MeO- 4%
m-MeO-	3-MeO- 35%, 4-MeO- 65%
p-MeO-	4-MeO-100%

Equation 2

In a series of reactions β-carbomethoxypropionyl chloride was treated with a wide variety of substituted diaryl cadmium reagents, it was found that only meta-dianisyl led to rearrangement (Equation 3).



X-o-Me-	X=2-Me-
m-Me-	3-Me-
p-Me-	4-Me-
o-Cl-	2-Cl
p-Cl	4-Cl-
1-naphthyl	1-naphthyl-
2-naphthyl	2-naphthyl-
o-MeO-	2-MeO-
m-MeO	* 4-MeO-
p-MeO-	4-MeO-

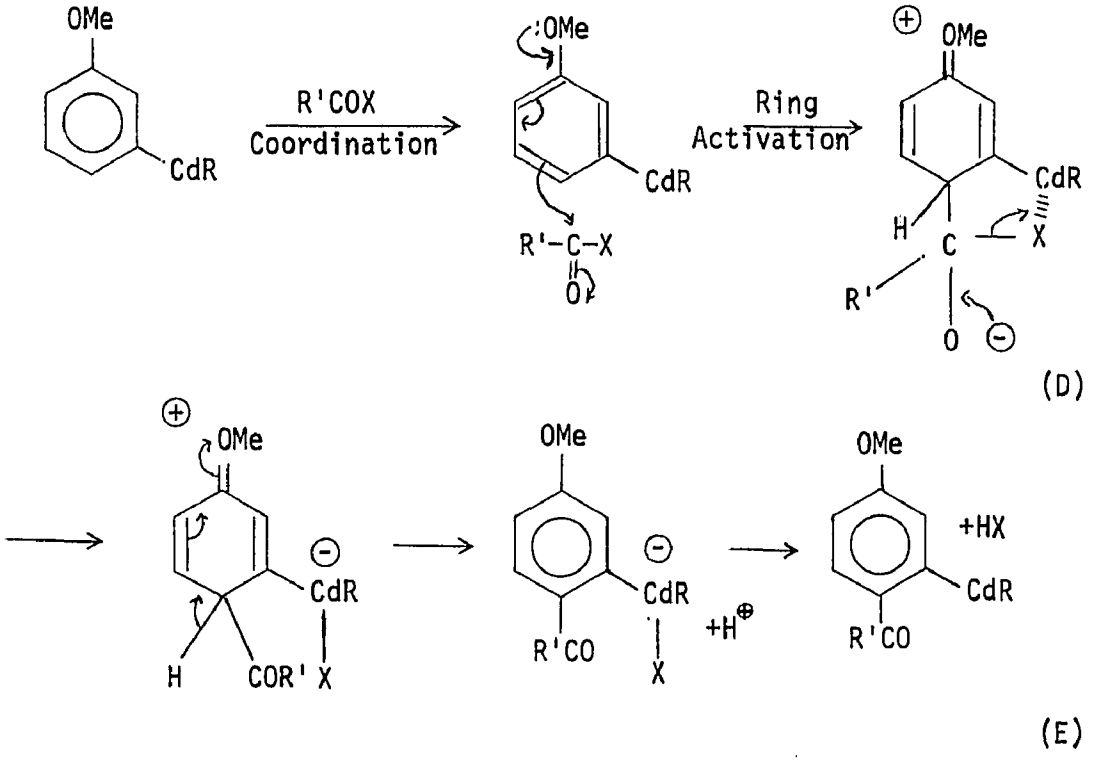
All in 100% isomeric purity

* Rearranged product

Equation 3

Dauben and Collette also found that the reaction of anhydrides with meta-dianisyl cadmium gave mixtures of "normal" and "abnormal" products.

The proposed mechanism is based on two reinforcing effects. First, the methoxy group powerfully activates its para position to electrophilic attack; and, second, the cadmium atom is acting as an internal Lewis acid to which the carbonyl substituent coordinates. This latter coordination renders the carbonyl more susceptible to nucleophilic attack by the aromatic ring and helps position the electrophile such that it can form a five-membered intermediate or transition state (D) (Scheme A).

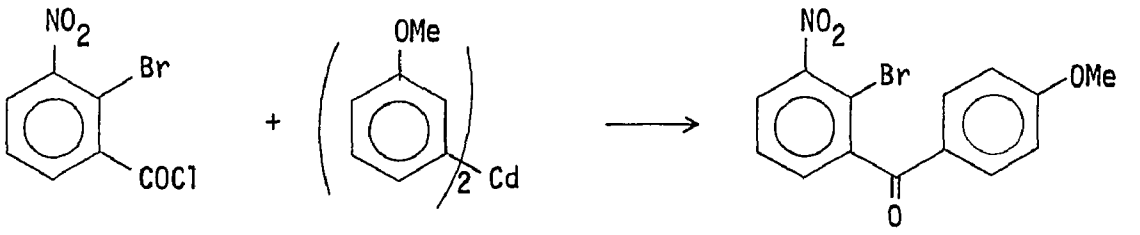


Scheme A

The intermediate E is visualized as reacting (in Equation 1) via a Michael-type reaction to produce the fluorenone A.

Soon thereafter, Martin and Walravens (3) reported that reaction of 2-bromo-3-nitrobenzoyl chloride with meta-dianisylcadmium gave only

2-bromo-4'-methoxy-3-nitrobenzophenone, (Equation 4). Nevertheless, reaction of ortho-, meta- and para-dianisylcadmium reagents with 3-nitrophthalic anhydride gave only the products expected; i.e., no abnormal products were noted.



Equation 4

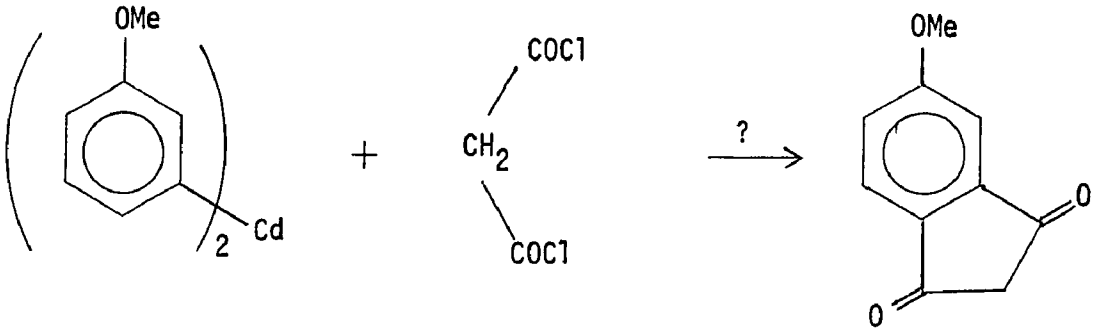
We decided to investigate the scope and mechanism of this unusual reaction of arylcadmium reagents further. The first step was to observe the effect the ring substituent has on the reaction products. Thus, the aryl cadmium reagents chosen for study were those containing the following meta- substituents: fluoro, trifluoromethyl, methyl, methoxy, thiomethoxy, and N,N-dimethylamino. The choice of these substituents reflects various ring-activating and -deactivating activities.

Second, if coordination of the carbonyl substituents is a major factor in the proposed mechanism, various acylating agents may produce diverse results. Consequently, acetyl chloride,acetyl bromide, acetic anhydride, and diacetyl sulfide were chosen.

Third, the electronic structure around cadmium may influence the extent of its coordinating ability, and hence the ratio of isomers. Therefore, in addition to diaryl cadmium reagents, the behavior of arylcadmium chlorides, bromides and iodides with acetyl chloride were to be explored.

An investigation into methods of verifying the proposed intermediate E was also to be included. En route to intermediate E hydrochloric acid is produced as a by-product. It seemed to us that this is incompatible with intermediate E and that the carbon-cadmium bond cannot exist if a true para-methoxyacetophenone compound containing a carbon-cadmium bond exists as in intermediate E.

Finally, we wanted to take advantage of the duality of the meta-dianisyl reagent in synthesis, one possibility being the reaction with malonyl dichloride to obtain 1,3-indanediones (Equation 5).



Equation 5

HISTORICAL

Introduction

The synthesis of ketones by way of organometallics has long been a major area of research. Currently transition metals are being probed as possible synthetic reagents for ketones. One of the most important organometallic intermediates for ketone synthesis is the organocadmium compound. These reagents have been used in synthesizing ketones ranging from asymmetric and radioactive compounds to large cholesteryl derivatives, and as routes to ketone intermediates to be further reacted. Because organocadmium reagents are often used in one step of a multistep process, they become buried in the literature.

There are a variety of reviews dealing with organocadmium reagents, most notably that of D. A. Shirley (4). This review covers the synthesis of ketones by the reaction of organic derivatives of magnesium, zinc and cadmium with acid halides reported up to the mid-1950's. Cason (5) had earlier written a review on organocadmium reactions with acid halides and anhydrides, and he discussed the factors involved in preparing and handling organocadmium reagents. Nesmeyanov and Kocheshkov (6) have written a practical review, in which they describe procedures for preparing and utilizing various types of organocadmium reagents. Although not a complete literature survey, it serves as a guideline for experimental work.

A chapter on organometallics, including a short section covering organocadmium reagents, has appeared in the review by Sonntag (7) on acid chloride reactions. Cois and Mandelbaum (8) prepared a short

survey of organocadmium reagents in 1966, although it is essentially a repetition of Shirley's earlier work, with a few current references included.

The intention here is to bring the synthesis of ketones by reaction of organocadmium reagents with acid halides up to date, and to include from Shirley's review the organocadmium reactions and combine them with current references to present a full review of past work. In addition, a section is included on the synthesis of ketones by way of anhydride reactions with organocadmium reagents.

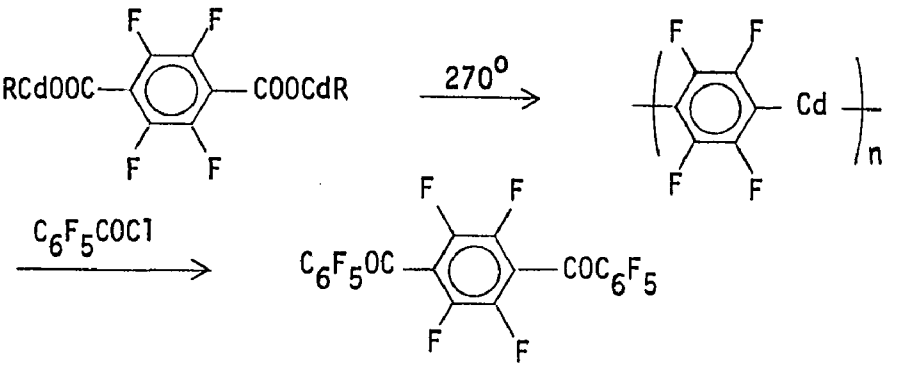
Synthesis

Organocadmium reagents are generally synthesized from the corresponding Grignard reagent, although lithium reagents have also been utilized. It has been stated in various references that the lithium reagent holds no advantage over the Grignard reagent as a precursor in organocadmium synthesis. In cases where Grignard reagents are difficult or impossible to prepare, however, the lithium route would be the method of choice.

The addition of anhydrous cadmium chloride to the Grignard reagent, best prepared from the alkyl or aryl bromide, has been performed at temperatures ranging from refluxing ether to Dry Ice-acetone. The choice here depends mainly on the stability of the cadmium reagent being formed; tertiary alkylcadmium reagents are unstable at room temperature, for example. It should be noted, however, that at 0^{o} the cadmium reagent often precipitates, and the mixture becomes a thick sludge. The usual method is to add the cadmium chloride with stirring to a mixture of the Grignard reagent in ether and then raise to reflux

temperature. To ensure the complete conversion of Grignard reagent to organocadmium a Gilman test is usually performed (9).

A new method (10) has been introduced to prepare arylcadmium reagents from cadmium carboxylate salts. These salts are thermalized at 270° to give what is proposed to be polymeric cadmium reagents (Equation 6).



Equation 6

When this is allowed to react with perfluorobenzoyl chloride. the para-dibenzoyl compound is produced in 39% yield. The proposed mechanism involves formation of radicals with subsequent loss of CO_2. This route may be of limited value since only the perfluoro aromatics have been used.

Direct preparation of organocadmium reagents from the metal has received some attention lately. It has been reported by Chenault and Tatibouet (11) that alkyl iodides or α,β-unsaturated bromides react with cadmium metal cuttings in DMSO, HMPT, and DMF. The metal reportedly dissolves rapidly in the solvent, which may account for its high reactivity (Equation 7). These authors found that the best

$$RI + Cd^0 \xrightarrow{HMPT} R_2Cd\cdot(HMPT)_2 \xrightarrow{R'COCl} RCOR'$$

R=Et,Pr,Bu
R'=Me,Et,Pr,Bu

Equation 7

yields were realized by using alkyl iodides in HMPT. They isolated the dialkylcadmium reagent by distillation and reported its structure as $R_2Cd \cdot (HMPT)_2$.

Cadmium, prepared by coprecipitation of its vapors in a solvent matrix, has been reported to react with ethyl iodide (12). Best yields were achieved when two molar equivalents of cadmium vapor were condensed at 77°K with diglyme. Products were quantified by hydrolysis with 10% HCl by use of vacuum line manipulations.

Reike has stated that with potassium metal reduction of cadmium salts leads to highly activated metal slurries that react with alkyl iodides in good yield (13).

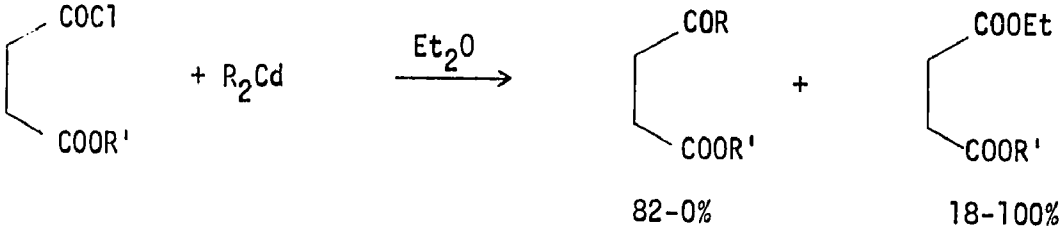
Nightingale and Wadsworth (14) reported the attempted conversion of phenylethynylmagnesium bromide to the corresponding cadmium reagent. After 1 hr of refluxing of ether, the Gilman test was still positive and reaction with acetyl chloride led to the carbinol. The preparation of phenylethynylcadmium and its reaction with acid chlorides have since been reported (15). In addition ethynylcadmium has been prepared and reacted with hexanoyl chloride in THF at 5° to give 75% of the n-pentyl ethynyl ketone (16).

Interestingly, it has been reported (17) that γ-benzyloxypropyl cadmium, when reacted with benzoyl chloride, gave no ketone. Although no explanation was given for this unexpected result, it would seem likely that the Grignard reagent may be the more troublesome intermediate, since reaction of cadmium reagents with ethers proceeds smoothly.

Solvent

The solvent of choice seems to be benzene which offers the advantages of higher yields, higher reaction temperature, fewer side products, and better homogeneity. The usual method is to distill most of the ether from the reaction flask, introduce benzene and continue distilling until the temperature reaches about 80^{o}, so as to replace about 75% of the ether (18). Some anomalies have been noted where a reaction in ether results in a better yield than that in benzene, but this is rare (19). It has been reported that high molecular weight organocadmium reagents react sufficiently slowly with acid chlorides such that acid chloride attack on the ether becomes a competitive reaction (20).

Various workers, but particularly Brunet (21) have observed that in reactions of diacid chlorides and acid chloride-esters in ether, a small to major portion of the products contains the ethoxy moeity from reaction with the solvent (Equation 8). The yields depend on the bulkiness of the organometallic group, as methyl and neo-pentyl reagents result in 82 and 0% keto ester, respectively.



Equation 8

Schweer and Schwarz (22) have studied cadmium reactions in various solvents in an attempt to maximize yields. Of toluene, xylene and mesitylene, only with toluene was a respectable yield observed

(60%, Me_2Cd with MeCOCl). Of the various polyethers studied the best yields were achieved with diethyleneglycol diethylether (73%, Me_2Cd with MeCOCl).

Dichloromethane has been used to a limited extent as a solvent for organocadmium reagents. Bentley (23) prepared a ketone derivative of thebaine in 80% yield with dipropylcadmium in H_2CCl_2. Although it was not mentioned, the choice of this solvent may be due to solubility problems of the acid chloride. Dichloromethane has also been used as a solvent for Grignard reagents (24). A noncoordinating solvent, it may impart abnormal properties on organocadmium reagents, but this possibility has yet to be explored.

The use of THF as a solvent has been done only in rare cases (16), because the ring is subject to cleavage by the organometallic reagent.

Mechanism

Inroads into the mechanism of organocadmium reactions have been made recently. It has been shown (25) that the presence of magnesium salts are needed for high yield preparations of ketones from acid chloride and organocadmium reagents. Although there is little difference in the reactivity of aliphatic acid chlorides, there is general agreement that aromatic acid chlorides do not react at all without magnesium salts present. The contrasting results for acetyl and benzoyl chloride are summarized in Equation 9.

	"in situ"	"purified"
$MeCOCl + Me_2Cd \longrightarrow MeCOMe$	80%	60%
$PhCOCl + Me_2Cd \longrightarrow PhCOMe$	40-50%	0%

Equation 9

It has been shown (26) that if one adds magnesium salts to "purified", salt-free organocadmium reagents, the reactivity of the R_2Cd is restored (Equation 10). These differences are more striking when

		"in situ"	"purified" + $MgBr_2$
$EtCOCl + Et_2Cd \longrightarrow$	EtCOEt	55%	55%

Equation 10

comparisons are made in the cadmium reactions with aldehydes (27). Michel and Henry-Basch (28) studied the addition of a variety of salts to "purified" organocadmium reagents, with the following results (Equation 11);

$PhCOCl + Bu_2Cd \longrightarrow$	PhCOBu	"purified"	0%
		$MgBr_2$	29%
		$ZnBr_2$	20%
		LiBr	5%

Equation 11

It has also been shown that lithium bromide, added to "purified", salt-free organocadmium reagents helps to increase their reactivity with acid chlorides, but to a lesser degree. Kollonitsch (29) has utilized this fact in a selective synthesis of α-keto esters. The cadmium reagent was inert to the chlorooxalate in the absence of magnesium salts; but when the magnesium salts were present, it reacted further to give α-hydroxyester. He found with the lithium salts the reaction was one of monosubstitution in reasonable yield (Equation 12). With oxalyl

$$ClCOCOEt + Bu_2Cd \xrightarrow[THF,\ -40^{o}]{LiBr} BuCOCOEt \quad (70\%)$$

Equation 12

chloride, the reaction to 1,2-diketone proceeded in 37% yield in the presence of lithium bromide (Equation 13).

$$ClCOCOCl + Bu_2Cd \xrightarrow[LiBr]{THF} BuCOCOBu \quad (37\%)$$
$$-50^{o}$$

Equation 13

Soussan and Freon (30) have shown that the reactivity of the organocadmium halide (RCdX) is inferior to that of the parent (R_2Cd), and that the presence of magnesium salts is important to the reactivities of both reagents (Equation 14).

$$EtCOCl + EtCdR'' \longrightarrow EtCOEt$$

R"	Yield
Et ("purified")	50%
Et ($MgBr_2$)	80%
Br ("purified")	30-35%
Br ($MgBr_2$)	45%

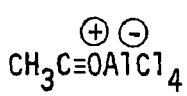
Equation 14

The purified EtCdBr was obtained by addition of one molar equivalent of cadmium bromide to the distilled diethyl cadmium, the ethylcadmium bromide being obtained by disproportionation. The authors also claim that the difference in reactivity is evidence for the presence of RCdX. There again, the difference in reactivities is more evident in the aldehyde reactions.

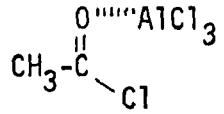
The composition of organocadmium halides has been reported from the analysis of crystals obtained by Tatibouet (31). He found the ratios to be 1:1:1:3 for Mg:Cd:R:X with two molecules of coordinated

ether. This is further evidence for the existence of RCdX.

Other salts have been added to "purified" organocadmium reagents in order to test their catalytic effect. Michel and Henry-Basch (28) obtained the oxonium salt (F) by addition of aluminum chloride to acetyl chloride in hexane. However, when the salt was isolated and dissolved in carbon tetrachloride, complex G was formed, as identified by infrared analysis (ν (C=O) 1598 cm^{-1}). They also found that when G was allowed



F



G

to react with dibutylcadmium in mesitylene or benzene, ketone was obtained in 60% yield (Equation 15).

$$Bu_2Cd + G \xrightarrow[\text{Benzene or Mesitylene}]{CCl_4} BuCOCH_3$$

Equation 15

The oxonium salt F remained unchanged in nitrobenzene (ν (C=O) 2305 cm^{-1}). When allowed to react with purified dibutylcadmium in benzene or mesitylene, it afforded 2-hexanone (40%) and, the Friedel-Crafts product (20%) (Equation 16).

$$R_2Cd + F \xrightarrow[\text{Benzene}]{PhNO_2} RCOCH_3 + CH_3COPh$$

Equation 16

In the presence of ferric chloride at room temperature, purified organocadmium reagents gave ketones in higher yields than the same

reaction with ferric chloride at low temperature (32). However, in the presence of magnesium salts and with inverse addition (19), the yields of ketones were not significantly different (Equation 17).

$$PhCH{=}CHCOCl + R_2Cd \longrightarrow PhCH{=}CHCOR \qquad \underline{FeCl_3} \quad 46\text{-}59\% \qquad \underline{MgX_2} \quad 40\text{-}65\%$$

Equation 17

Ashby and Sanders (33) have attempted to define the composition of the organocadmium reagent. Through elegant infrared and elemental analyses, the authors have shown that RCdX exists in solution and that $MCdX{\cdot}MgX_2$ exists in a crystalline form, when CdX_2 and the Grignard reagent are allowed to react in a 1:1 ratio. Infrared evidence points out the fact that magnesium salts complex with both the organocadmium reagent and the acid chloride. However, it is not known which complexing accounts for the major portion of reactivity.

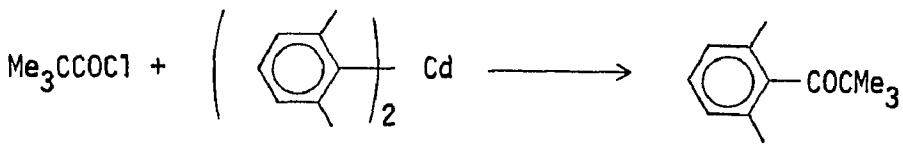
When the Grignard reagent and cadmium chloride were added in a 2:1 ratio, only diorganocadmium and magnesium halide resulted. It was also shown that organocadmium reagents can not be kept for long periods of time, unless kept in the cold and in the absence of light, because cadmium metal is deposited.

Reactions

Far and above the most exploited reaction of organocadmium reagents is that with acid halides. In general, these reactions are performed on acid chlorides, in part because acid bromides are more highly subject to hydrolysis and the product yields are not much higher. Since Shirley's review, the types of acid chlorides and cadmium reagents have expanded a great deal, including sterically hindered and radio-

actively labelled compounds and compounds containing interesting functionalities.

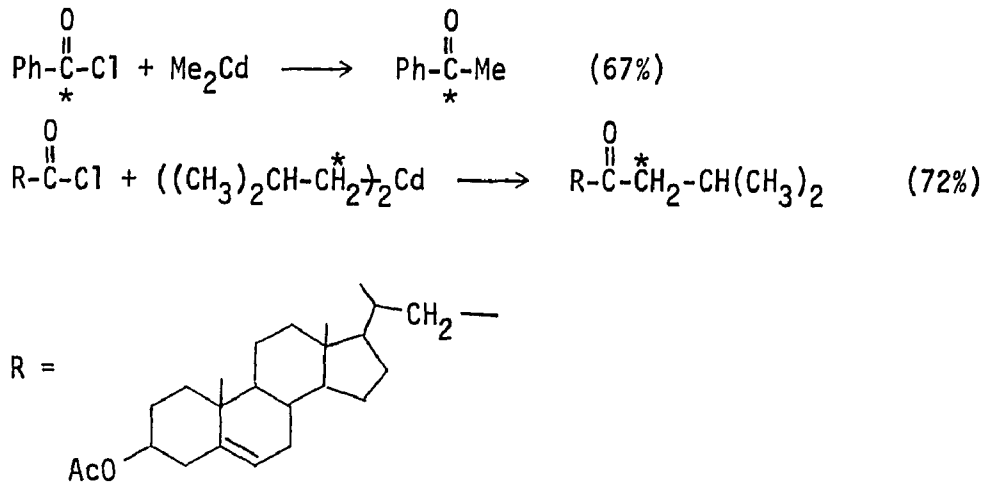
An example of a reaction with sterically hindered reagents is given in Equation 18. Pivaloyl chloride reacts with di-2,6-dimethyl



Equation 18

phenylcadmium to produce the corresponding ketone in 50% yield (34). With acetyl chloride, the yield of acetophenone product is 63%. The remarkable success of reactions of sterically hindered systems has apparently not been exploited, for there is a paucity of information on this subject.

Radioactively labelled acid chlorides (35) and labelled cadmium reagents (36) have been utilized with success (Equation 19).



Equation 19

Cost-to-yield ratios are very important in these reactions and conditions are usually adjusted to ensure the maximum efficiency.

Study of acid chlorides with substituents that are reactive toward most organometallic reagents has also been expanded in the past twenty years. α- (37) and β- (38) chloroacid chlorides afford no unexpected side products (Equation 20). The fact that there is no elimination from the β-chloro compounds points up the fact that organo-

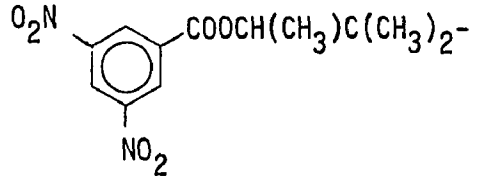
$$CH_3\text{-}CHCl\text{-}COCl + \underline{n}\text{-}Bu_2Cd \longrightarrow CH_3CHClCO\text{-}\underline{n}\text{-}Bu$$

$$ClCH_2CH_2COCl + \underline{i}\text{-}Bu_2Cd \longrightarrow ClCH_2CH_2CO\text{-}\underline{i}\text{-}Bu$$

Equation 20

cadmium reagents are not as basic as would be expected. Other interesting acid chlorides that have been used with success are esters, from the parent hydroxyacid chloride (39), and β-ethers (40) (Equation 21 and 22 respectively).

$$RCOCl + \underset{\text{Large Excess}}{Me_2Cd} \longrightarrow RCOMe \quad (22\%)$$

R= 

Equation 21

$$R\text{-}O\text{-}CH_2CH_2\text{-}COCl + Ph_2Cd \longrightarrow R\text{-}O\text{-}CH_2CH_2COPh$$

R	%Yield
Me	90
Et	82
n-Pr	82
i-Pr	89
n-Bu	91

Equation 22

A reaction that proceeds with decarbonylation (See Equation 30) is that of triphenylacetyl chloride (41). At ratios of 2:1 (organocadmium to acid chloride) 12-46% yields of ketone were observed, with 33-13% of subsequent hydrocarbon (Equation 23). However, at

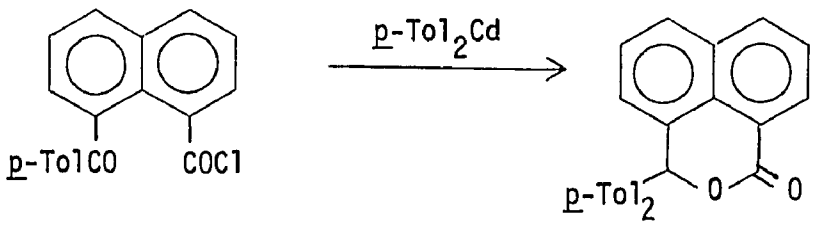
$$R_2Cd + Ph_3CCOCl \longrightarrow Ph_3CCOR + Ph_3CR$$

R	Ratio	Ketone	Hydrocarbon
Me	2:1	12	33
Me	5:1	73	11
Et	2:1	40	13
n-Bu	2:1	46	18
n-Bu	5:1	63	11

Equation 23

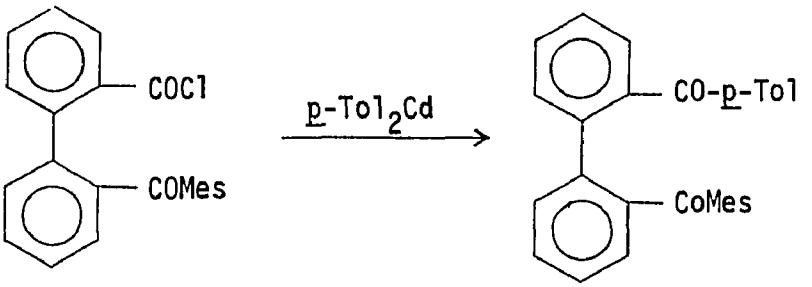
ratios of 5:1 the yield of ketone was 63-73%. The trityl radical is most likely an intermediate here, with subsequent chain reaction involving the organometallic. Perhaps with excess cadmium reagent coordination of the carbonyl oxygen is amplified to the point where the carbonyl carbon is so highly electrophilic that its attack is kinetically the route of choice.

Ketoacid chlorides have been allowed to react with cadmium reagents in order to obtain diketones. In many cases (42), however, the initial attack leads to cyclization (Equation 24). If the substrate



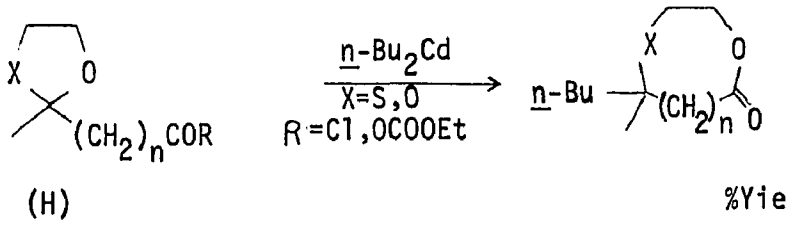
Equation 24

can not cyclize to a 5- or 6-membered ring, then diketo products can be obtained (Equation 25).



Equation 25

Attempts to prepare diketo compounds through the use of 1,3-dioxane or 1,3-thioxane derivatives of ketoacid chlorides have been explored. It has been shown (43) however, that these protecting groups do not survive the conditions of organocadmium reactions when n=2 and instead lead to 1,3-dioxo-4-keto ring systems (Equation 26). However,

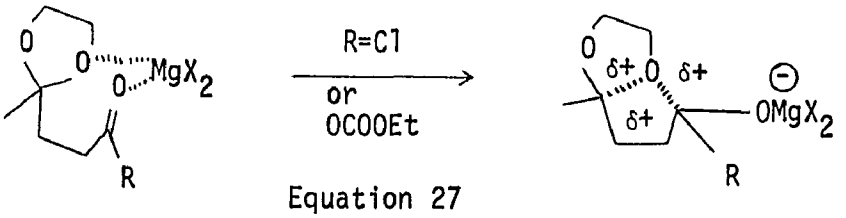


	n=2	
R	Cl	OCOOEt
X	O	S
%Yield	44	39

Equation 26

when 1,3-dithianes are used, the reaction to the protected ketone proceeds smoothly.

The authors proposed that magnesium salts coordinate with the ketal oxygen and the carbonyl to form a 7-membered ring as shown in Equation 27. When salt-free dimethyl cadmium was employed, only the



Equation 27

ethyl ester (H, R=OEt) was formed from the acid chloride or mixed anhydride. When the next lower homolog (Equation 26, n=1, R=OCOOEt) was used, no opening of the ketal was observed and the protected diketone was formed in 47% yield.

Table I contains a list of all the acid chloride-cadmium reactions which could be found in the literature up through early 1978. As has been mentioned, some other reactions may be buried in the literature as one step in a multistep process. The entries are arranged in Table I according to the complexity of the cadmium reagent and then subdivided according to the complexity of the acid chloride. References preceded by "S" refer to those that have been quoted from Shirley's review (4). The reader is advised to consult that volume for the exact literature citation.

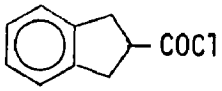
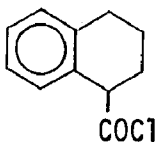
TABLE I

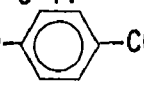
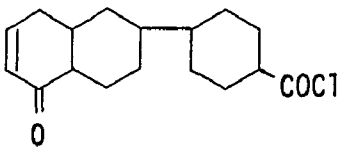
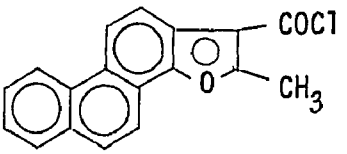
The Reactions of Acid Chlorides with Organocadmium Reagents

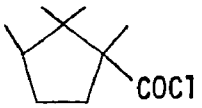
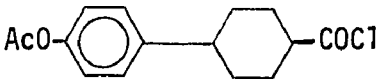
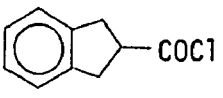
$$R'COCl + R_2Cd \longrightarrow R'COR$$

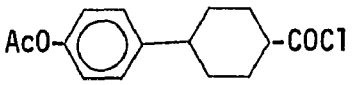
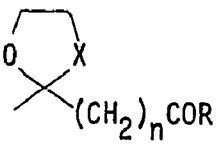
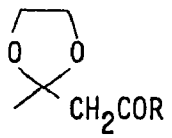
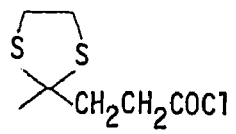
R = Me

R'COCl	%Yield	Remarks[d]	References
CH_3COCl	60	in toluene	22
CH_3COCl	23-31	in xylene	22
CH_3COCl	21-33	in mesitylene	22
CH_3COCl	73	in diethylene glycol diethyl ether	22
CH_3COCl	46	in diethylene glycol dibutyl ether	22
$CH_3\overset{*}{C}OCl$	64	in diethylene glycol diethyl ether	22
$CH_3CH_2\overset{*}{C}OCl$	52	in diethylene glycol diethyl ether	22
3-Thienyl-COCl	81	----	S69
$(CH_3)_3CCH_2CH_2COCl$	40-50	----	44
$PhCOCl$	85	----	S81
$Ph\overset{*}{C}OCl$	67	----	35
o-ClPhCOCl	XX[a]	----	45
2,6-D_2PhCOCl	78	----	46
$CH_3CH_2CH_2C(CH_3)(C_2H_5)$-COCl	47	----	S103
C_6F_5COCl	56	----	47
o-MePhCOCl	XX,84	----	45,46

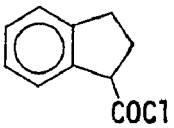
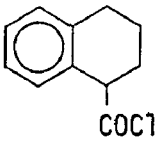
R'COCl	%Yield	Remarks	References
m-MePhCOCl	XX,83	----	S50,S9
p-MeOPhCOCl	84	----	S9
m-CF_3PhCOCl	91	----	47
p-FPhCH_2COCl	XX	----	48
m-AcPhCOCl	85	----	64
2-Me,6-MeOPhCOCl	33	----	50
2-Me,3-MeOPhCOCl	85	----	51
2,3-Me_2PhCOCl	71	----	S105
3,5-$(MeO)_2$PhCOCl	84	----	S105
m-MePhCH_2COCl	XX	----	48
p-MePhCH_2COCl	XX	----	48
m-MeOPhCH_2COCl	XX	----	48
p-MeOPhCH_2COCl	XX	----	48
PhCH_2CH_2COCl	69	----	S104
m-ClPhCH_2CH_2COCl	33	as MeCdCl	52
Ph$CH_2CH_2CH_2$COCl	78	----	S113
	XX	as MeCdCl	52
	XX	±	S117
	65	±	S117
1-Naphthyl-CH_2COCl	67	----	53

R'COCl	%Yield	Remarks	References
1-Tetralin-CH_2COCl	69	±	S117
$Ph_2CHCOCl$	XX	----	54
cyclo-$C_6H_{11}CHPhCOCl$	49	±	55
$PhCH_2O$-  -COCl	96	----	56
$CH_3(CH_2)_{14}COCl$	55	----	S129
$Ph(CH_2)_9COCl$	40	----	57
	13	----	S130
	98	as MeCdBr	58
Ph_3CCOCl	73	11% Ph_3CMe	41
	R = Et		
MeCOCl	50	as EtCdBr	S9
MeCOCl	80,46	60% in absence of MgX_2 salts	25,S9
EtCOCl	55	55% when reconstituted	36
$Cl(CH_2)_3COCl$	78	----	59
2-Furyl-COCl	61	----	S9
$CH_3(CH_2)_3CHClCOCl$	XX	----	61
$Et_2CHCOCl$	45	----	62
Me_3CCH_2COCl	40-50	----	63
PhCOCl	40-50	trace in absence of MgX_2 salts	25
m-AcOPhCOCl	92	----	64

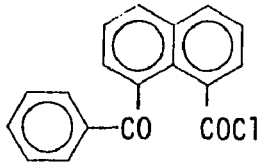
R'COCl	%Yield	Remarks	References
o-Tolyl-CH_2COCl	65-70	----	S19
	95	±	S40
$Ph_2CHCOCl$	XX	----	52
	63	±	S123
$CH_3(CH_2)_{16}COCl$	62	----	S53
8-Benzoyl-1-naphthyl-COCl	0	95% lactone	42
Ph_3CCOCl	39	18% $Ph_3CCH_2CH_3$	41
8-(3,4-Me_2Ph)-1-naphthyl-COCl	38	----	42
8-Mesitoyl-1-naphthyl-COCl	51	----	42
$CH_3(CH_2)_4COCl$	75	$(HC\equiv C-)_2Cd$ in THF at 5°	16
$RCOCl$[c]	XX	$(PhC\equiv C-)_2Cd$	15
	R = Pr[e]		
Me_3CCH_2COCl	40-50	----	61
3-Pyridyl-COCl	30	----	S93
m-AcOPhCOCl	83	----	64
3,4-$(MeO)_2$-PhCOCl	85	----	65
$PhCH_2CH_2COCl$	62	----	52
	75	as n-PrCdCl	52
$Ph_2CHCOCl$	XX	----	54
$CH_3CH_2CH_2COCl$	60	i-Pr_2Cd	S9
$Ph_2CHCOCl$	XX	i-Pr_2Cd	54

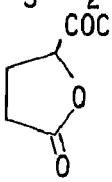
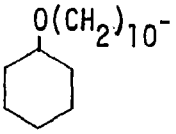
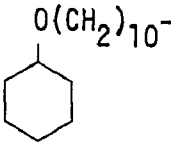
R'COCl	%Yield	Remarks	References
	74	±	S124
	R = Bu(e)		
CH_3COCl	74	----	S9
$ClCH_2COCl$	26,51	----	S49,S19
CH_3COCl	17	tert-Bu_2Cd	S9
$CH_3CHClCOCl$	43	----	S19
$ClCH_2CH_2COCl$	10	i-Bu_2Cd	38
Me_3CCH_2COCl	40-50	i-Bu_2Cd	63
$Me_3CCH_2CH_2COCl$	40-50	----	44
	0	all 4-keto-1,3-dioxo structures n=1,2 X=O,S R=Cl,OCOOEt	43
	47	R=OCOOEt	43
	17	----	43
$3,5\text{-}(MeO)_2PhCOCl$	27	----	S37
$3,4,5\text{-}(MeO)_3PhCOCl$	29	----	66
m-AcOPhCOCl	83	----	64
m-AcOPhCOCl	70	i-Bu_2Cd	64

R'COCl	%Yield	Remarks	References
$Ph_2CHCOCl$	XX	----	54
8-Benzoyl-1-naphthyl-COCl	0	99% lactone	42
8-(2,6-Me_2Ph)-1-naphthyl-COCl	83	----	42
8-Mesitoyl-1-naphthyl-COCl	85	----	42
Ph_3CCOCl	62	18% Ph_3CBu	41
p-NCPhCOCl	11	$(3\text{-Butenyl})_2Cd$	67
BuCOCl	55	$(EtOCH_2)_2Cd$	59
PhCOCl	13	$(EtOCH_2)_2Cd$	59
	R = Pent[e]		
$ClCH_2COCl$	24	----	S47
$CH_3CHClCOCl$	XX	----	61
m-AcOPhCOCl	86	----	64
m-AcOPhCOCl	78	i-$Pent_2Cd$	64
	R = Hexyl[e] Phenyl		
Me_3CCH_2COCl	47	----	68
m-AcOPhCOCl	70	----	64
$CH_3CH_2CH_2COCl$	45	3-iso-$hexenyl_2Cd$	S9
MeCOCl	83	----	S9
MeCOCl	83	as PhCdCl	S9
EtCOCl	76,80	----	S9,S11
$MeOCH_2CH_2COCl$	90	----	70
$EtOCH_2CH_2COCl$	82	----	70
$PrOCH_2CH_2COCl$	82	----	70
n-$BuOCH_2COCl$	89	----	70

R'COCl	%Yield	Remarks	References
t-$BuOCH_2COCl$	91	----	70
PhCOCl	57	----	S9
m-MeOPhCOCl	56	----	71
	XX	±	72
	51	±	73
3-Br-2,4,6-Me_3PhCH_2COCl	87	as PhCdCl	S26
2,4,5,6-Me_4PhCH_2COCl	47	as PhCdCl	S26
2,3,5,6-Me_4PhCH_2COCl	93	as PhCdCl	S26
2,4,6-Et_3PhCH_2COCl	33	as PhCdCl	S26
8-Benzoyl-1-naphthyl-COCl	60	----	42

Higher Homologs

R	R'COCl	%Yield	Remarks	References
p-ClPh	m-ClPhCOCl	XX	----	74
n-Hept	$CH_3(CH_2)_6COCl$	77	----	75
n-Hept	3,4-$(MeO)_2PhCOCl$	41	----	65
p-Toluyl	8-Toluyl-1-naphthyl-	0	pseudo-phthalide	42
p-Toluyl		38	----	42
$PhCH_2$	MeCOCl	18	----	S9
$PhCH_2$	p-$ClPhCH_2COCl$	86	----	76

R	R'COCl	%Yield	Remarks	References
$PhCH_2$	p-$MeOPhCH_2COCl$	60	----	76
$CH_3(CH_2)_7$	$CH_3(CH_2)_5COCl$	20	----	78
2,6-Me_2Ph	MeCOCl	62	----	34
2,6-Me_2Ph	Me_3CCOCl	50	----	34
p-$MeOPhCH_2$	p-$MeOPhCH_2COCl$	0	Cd^0 and coupling product	76
$PhCH_2CH_2$	$CH_3(CH_2)_{16}COCl$	66	----	S55
$CH_3(CH_2)_8$	$CH_3(CH_2)_4COCl$	17	----	77
$CH_3(CH_2)_9$	$CH_3(CH_2)_3COCl$	40	----	77
$CH_3(CH_2)_9$		34	calculated from the acid	78
$PhCH_2OCH_2CH_2CH_2$	PhCOCl	0	----	17
$CH_3(CH_2)_{10}$	$CH_3(CH_2)_2COCl$	43	----	77
$CH_3(CH_2)_{11}$	$ClCH_2COCl$	18	----	S47
$CH_3(CH_2)_{11}$	CH_3CH_2COCl	38	----	77
$CH_3(CH_2)_{13}$	$ClCH_2COCl$	15	----	S47
$CH_3(CH_2)_{13}$	MeCOCl	55	----	77
$CH_3(CH_2)_{15}$	$ClCH_2COCl$	33	----	S19
	$CH_3(CH_2)_{21}COCl$	12	----	S143
	$CH_3(CH_2)_{25}COCl$	15	----	S143

(a) XX=No reported yield
(b) See Equation 21
(c) R is not reported
(d) ± = racemic
(e) n-, unless otherwise noted

Diketones have been prepared from diacid chloride and organocadmium reagents. The best yields have been recorded for adipyl dichloride (79) and the higher homologs (Equation 28). As has been

$$ClCO\text{-}(CH_2)_nCOCl + R_2Cd \xrightarrow{n\geq 4} RCO\text{-}(CH_2)_n\text{-}COR$$

Equation 28

mentioned, Kollonitsch (29) prepared the 1,2-diketone (n=0, R=Bu) from oxalyl chloride and the cadmium reagent in the presence of lithium bromide in a 37% yield at -50° in THF. In the "normal" case oxalyl chloride undergoes triple addition with formation of α-hydroxyketone (80) in 22% yield (Equation 29). Even at low temperatures in hydrocarbon

$$ClCO\text{-}COCl + Bu_2Cd \longrightarrow Bu\text{-}\overset{\overset{OH}{|}}{\underset{\underset{Bu}{|}}{C}}\text{-}COBu$$

Equation 29

solvents with inverse addition, the yields of 1,2-diketone never exceeded 12%. Monoketones, however, were formed in 21-33% yields from a decarbonylation reaction (81) (Equation 30). Renson and Beetz (82)

$$ClCO\text{-}COCl \xrightarrow{R_2Cd} R\text{-}CO\text{-}COCl \xrightarrow{-CO} R\text{-}COCl \longrightarrow R\text{-}COR$$

Equation 30

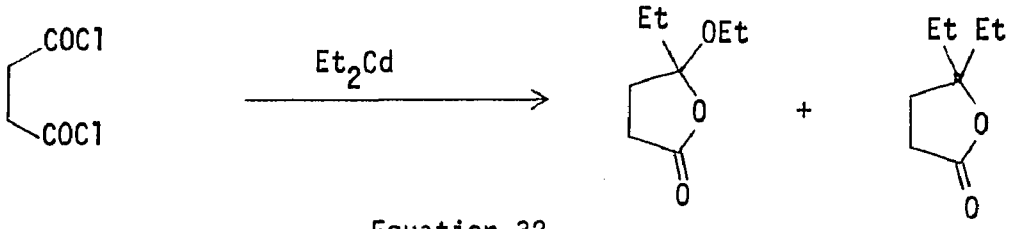
reported that reaction of malonyl dichloride with organocadmium reagents afforded diketones in yields ranging from 26-43% (Equation 31).

$$ClCOCH_2COCl + R_2Cd \longrightarrow RCOCH_2COR$$

R	Yield
Et	36
n-Pr	31
n-Bu	43
n-Pent	26
n-Hex	21

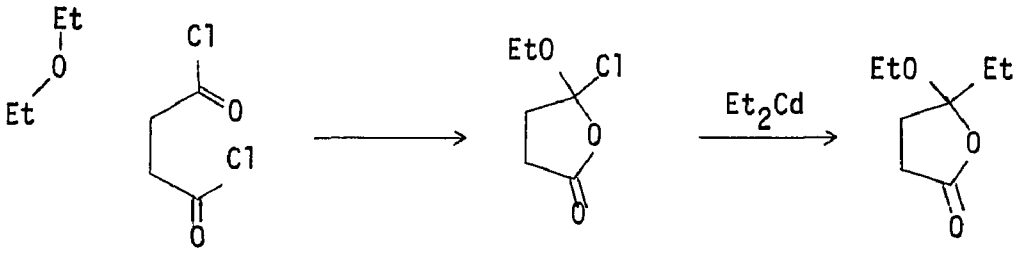
Equation 31

When n=2 (83), the main products were cyclic pseudoesters and lactones (Equation 32). It was suggested that these arose from initial attack by the ether solvent on one of the acid chlorides, which then



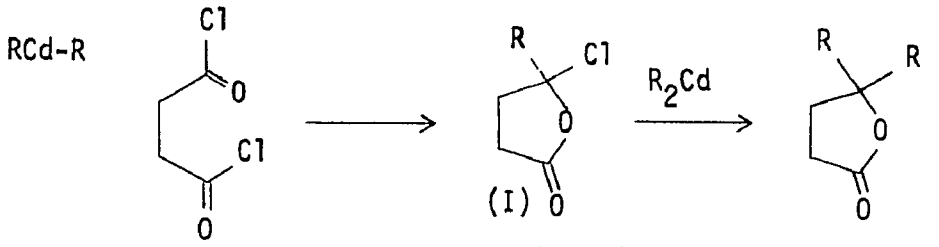
Equation 32

lactonized; the resultant 1-chlorolactone was attacked by the cadmium reagent (Equation 33). The lactone arose from initial attack of the



Equation 33

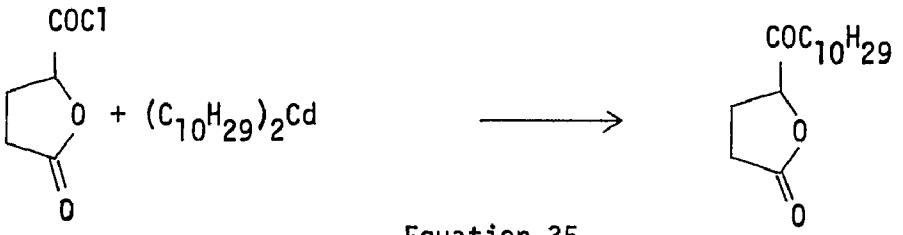
acid chloride by the cadmium reagent followed by lactonization and chloride substitution (Equation 34).



Equation 34

When glutaryl dichloride was allowed to react with cadmium reagents (84), no pseudoester was isolated. Instead, the main product was the 1-chlorolactone (I) obtained in a manner similar to equation 34. 1,4-Diketones were isolated in a low but significant yield (6-10%). Interestingly, the inertness of γ-lactones to organocadmium reagents (78)

has been utilized in a synthesis of furans in 34% yield (Equation 35). Table II lists the diacid chlorides that have been used as substrates with organocadmium reagents.



Equation 35

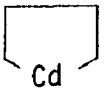
Another strategy for obtaining diketones from cadmium reagents (85) has been to employ the dicadmium halides with two molar equivalents of acid chloride (Equation 36). Best yields were obtained when n=5,6 or 10.

$$XMg\text{-}(CH_2)_n\text{-}MgX + CdCl_2 \longrightarrow ClCd\text{-}(CH_2)_n\text{-}CdCl \xrightarrow{2\text{-}RCOCl} RCO(CH_2)_nCOR$$

Equation 36

When n=4 or 8 the yields were on the order of 10-20%. Secondary reactions were possible, and blackening of the reaction medium in air was noted.

In the course of their work, Sousson and Freon (86) have explored the reaction of 1,4-di-Grignard reagents of 1,4-dibromobutane with one molar equivalent of cadmium chloride. By distillation, they isolated a compound in 20% yield claimed to be the cyclic 5-membered ring, (J). Its



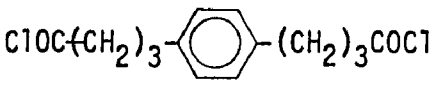
(J)

molecular weight was found to be 218; (calc:182.76); it reacted to give ketones at a much faster rate than the organocadmium reagent obtained from the 1:2 (Grignard to cadmium chloride) compound. When this

TABLE II

Reactions of Diacid Chlorides with *in situ* Organocadmium Reagents

$$ClCO\text{-}R'\text{-}COCl + R_2Cd \xrightarrow[\text{benzene}]{\text{ether}} RCO\text{-}R'COR$$

R	ClCO-R'-COCl	Yields[a]	Remarks	References
Me	$(CH_2)_4(COCl)_2$	15	38% in benzene	79
Me	$(CH_2)_5(COCl)_2$	60	28% hydroxyketone 6% dialcohol	87
Me	$(CH_2)_8(COCl)_2$	59	-----	88
Et	ClCOCOCl	0	21% hydroxyketone	81
Et	$CH_2(COCl)_2$	36	other products	82
Et	$(CH_2)_3(COCl)_2$	6-10	30-40% chlorolactone 15-20% lactone	84
Et	$(CH_2)_4(COCl)_2$	80	-----	89
Et	$(CH_2)_4(COCl)_2$	68	55% in benzene	79
Et		74	-----	90
n-Pr	ClCOCOCl	3	25% hydroxyketone 14% monoketone	81
n-Pr	$CH_2(COCl)_2$	31	other products	82
n-Pr	$(CH_2)_4(COCl)_2$	79	70% in benzene	79
n-Bu	ClCOCOCl	37	purified LiBr added	29
n-Bu	$CH_2(COCl)_2$	43	other products	82
n-Bu	$(CH_2)_4(COCl)_2$	90	88% in benzene	79
n-Bu	$(CH_2)_4(COCl)_2$	65-70	-----	89
n-Pent	ClCOCOCl	0	23% hydroxyketone 17% monoketone	81
n-Pent	$CH_2(COCl)_2$	26	other products	82

R	ClCO-R'-COCl	Yield[a]	Remarks	References
n-Pent	$(CH_2)_4(COCl)_2$	90	91% in benzene	79
n-Hex	ClCOCOCl	0	20% hydroxyketone 22% monoketone	81
n-Hex	$CH_2(COCl)_2$	21	other products	82
Ph	$COCl_2$	XX	-----	91,92
Ph	$(CH_2)_4(COCl)_2$	75	-----	89
Ph	2,2'-Biphenylene-$(COCl)_2$	83	-----	63
$PhCH_2CH_2$	$(CH_2)_8(COCl)_2$	65	-----	93

(a) XX=unreported yields

"cyclic compound" was treated with benzoyl chloride, the dibenzoyl compound was obtained in 10-15% yields. As has been stated, aromatic acid chlorides do not react with cadmium reagents in the absence of magnesium salts. Thus the authors point to its reactivity as a basis for the structure of the cyclic cadmium reagent. It should be mentioned that spectrophotometric data were not reported as confirmatory evidence.

Other diacid derivatives as starting materials have been allowed to react with organocadmium reagents such as the acid chloride-esters (K). These reactions have been known for some time, but usually only the long-chain compounds have been reported (K, $n \geq 3$).

$$ClCO\text{-}(CH_2)_n\text{-}COOR$$

K

When n=0, the main products from the reaction with dialkylcadmium reagents are the α-hydroxyesters, obtained from double addition (94), similar to the diacid chlorides (Equation 29). However, it was reported that the reaction of o- and p-tolylcadmium reagents, added inversely, to ethyl chlorooxalates gave α-ketoesters in 50 and 22% yields, respectively (95), (Equation 37).

$$EtCOCOCl + R_2Cd \longrightarrow RCOCOEt$$

R = o- and p-tolyl

Equation 37

Although no yields were reported (96), the reaction of the acid chloride-ester from malonic acid (K, n=1) with cadmium reagents was reported to give the corresponding keto esters (Equation 38).

$$EtOOC\text{-}CH_2\text{-}COCl \xrightarrow{R_2Cd} EtOOC\text{-}CH_2\text{-}COR$$

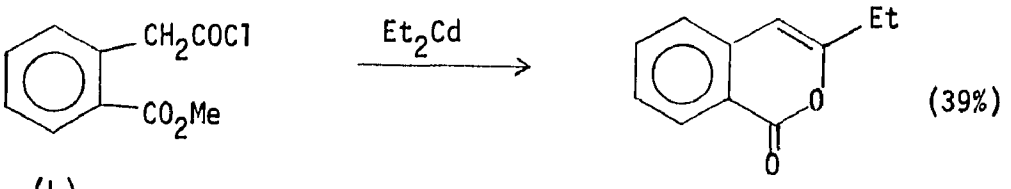
R=Et, n-Bu, n-Oct

Equation 38

French workers (21) have reported that the reaction of acid chloride-esters derived from succinic acid when stirred in ether gave significant yields of succinate and in some cases cyclic lactones. Here again, succinate appears to have arisen from attack by the ether (see Equations 32 and 33). Results of this type seem to be unique in that no other authors have reported such side products when working with succinate acid chloride esters; however, as has been mentioned, this side reaction is common for diacid chlorides.

When the dimethyl- and diethylcadmium reagents were reacted with succinate acid chloride-esters in diisopropyl ether, the γ-ketoesters resulted in 50% and 63% (97) yields, respectively.

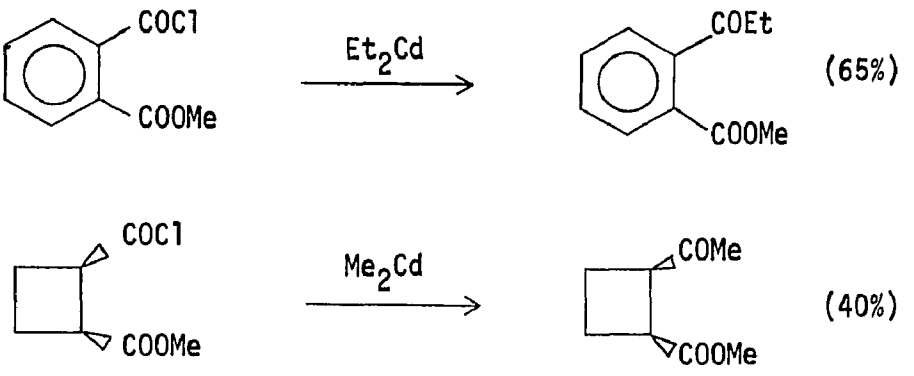
Huisgen and Ravenbusch (98) have reported the reaction of diethylcadmium with the 1,2-phenylene acid chloride-ester (L) (Equation 39). Here the cadmium reagent attacks the acid chloride and causes cyclization



(L)

Equation 39

with subsequent loss of HCl. However, with the phthalic acid chloride-ester or with cis-1,2-bicyclobutyl acid chloride-ester (99) no cyclization takes place (Equation 40).



Equation 40

When phosgene and ethyl or phenyl chloroformate were allowed to react with diphenylcadmium (91), the only products reported were, respectively, benzophenone and ethyl benzoate or phenyl benzoate. However, when aliphatic cadmium reagents were used with the chloroformates, no esters could be isolated (Equation 41).

$$ClCOCl + Ph_2Cd \longrightarrow PhCOPh$$

$$ClCOX + Ph_2Cd \longrightarrow PhCOX \qquad X=OEt,OPh$$

Equation 41

A summary of the acid chloride-esters used in these reactions is presented in Table III.

Asymmetric compounds have been used as precursors for organocadmium reactions. McDonnell and Davis (117) obtained a mixture of endo- and exo- bicycloacetyl compound, 65%:35%, respectively, in a total of 51% yield from the endo-bicyclic compound (M) and dimethylcadmium (Equation 42). It was assumed that magnesium salts isomerized the

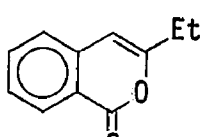
TABLE III

Reactions of Acid Chloride-Esters with Organocadmium Reagents

$$R_2Cd + R'OOC-(CH_2)_n-COCl \longrightarrow R'OOC-(CH_2)_n-COR$$

R' = Me or Et

R	n[a]	%Yield[b]	Remarks	References[c]
Me	2	82	18% succinate	21
Me	4	59,76	----	S100,S46
Me	2-(3-Me,3-Et)	40	(-) both isomers (functional exchange)	100
Me	7	64	----	S100
Me	8	76,84	----	101,S46,S19
Me*	11	85	radioactive Me^*_2Cd	102
Me	(d)	62	----	103
Et	1	XX	----	98
Et	2	46	----	104
Et	2	80	20% succinate	21
Et	2	0	lactone formation	83
Et	2	63	isopropyl ether as solvent	97
Et	3	77	----	105
Et	3	58	as EtCdBr	106
Et	4	54	----	107
Et*	4	XX	radioactive $(CH_3C^*H_2)_2Cd$	108
Et	2-(2,3-dimethyl)	42	----	109

R	n	%Yield	Remarks	References
Et	homophthalic	0	39% 	98
Et	8	88	----	S122
n-Pr	2	42	38% succinate	21
n-Pr	2-(3,3-dimethyl)	83	----	110
n-Pr	3-(4,4-dimethyl)	71	----	101
n-Pr	7	95	----	S122
i-Pr	2	29	71% succinate	21
i-Pr	7	10	----	112
n-Bu	0	4	----	95
n-Bu	1	XX	----	96
n-Bu	2	45,80	----	S19
n-Bu	3-(3Et,3-n-Bu)	91	----	S12
i-Bu	0	7	----	95
tert-Bu	2	32	32% succinate	21
2-MeBu	2	60	----	S46
i-Pent	2	41,44	----	S19,S107
i-Pent	2	73-79	----	S19,S46,S62
i-Pent	4	45	----	S115
i-Pent	8	85	----	S46
sec-Pent	2	10,22	----	S19,S46
neo-Pent	2	0	100% succinate	21
cyclo-Pent	2	21	79% succinate	21
n-Hex	2	26	74% succinate	21
n-Hex	2-(2,3-dimethyl)	62-74	----	107
n-Hex	3-(3,3-dimethyl)	78	----	107
Ph	8	40	----	93

R	n	%Yield	Remarks	References
Ph	(f)	68	----	S142
o-ClPh	2	32	----	S110
p-ClPh	2	40	----	S110
m-BrPh	4	50	----	113
o-Tolyl	0	50	----	95
o-Tolyl	2	58	----	S110
p-Tolyl	0	22	also hydroxyester	95
p-Tolyl	2	56	----	S110
m-Tolyl	2	62	----	S110
o-Anisyl	2	43,50	----	S40,S126
m-Anisyl	2	27	----	S110
p-Anisyl	2	54	----	S110
n-Oct	1	XX	----	96
n-Oct	6	62	----	114
n-Oct	7	45	----	S122
4-Et-Hex	7	45	----	S134
$PhCH_2CH_2$	8	79	some coupling product	93
7-Me-Oct	7	55	----	S135
4-Me-Oct	8	54	----	S136
6-Me-Oct	8	77	----	S46
$PhO(CH_2)_4$	1,2-Phenylene	52	----	98
3-Me-Nonyl	7	43	----	S136
4-Me-Nonyl	7	46	----	S136
5-Me-Nonyl	8	65	----	S141
8-Me-Nonyl	8	46	----	S107
6-Et-Oct	7	49	----	S134

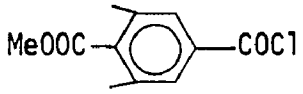
R	n	%Yield	Remarks	References
1-Naphthyl	2	64	----	S110
2-Naphthyl	2	34	----	S110
6-MeO-1-naphthyl	2	44	----	49
Undecyl	3	82,79	----	S126,114
4-Me-Undecyl	5	49	----	S135
5-Me-Undecyl	5	52-56	----	S140
n-Tridecyl	3-(2,2-dimethyl)	88	----	S139
4-Me-Tridecyl	3	40	----	S135
n-Tetradecyl	2-(2-Me)	64	----	S139
9-n-Prdodecyl	7	72	----	S122
4-Me-tetradecyl	2	38	----	S136
4-Me-tetradecyl	8	78	----	S144
n-Hexadecyl	8	32	----	S143
n-Hexadecyl	16	79	----	S39
n-Octadecyl	5	39	----	S129
9-Octadecenyl	4-(3-Me)	41	----	115
Nonadecyl	3-(3-Me)	80	----	S129
Heneicosyl	10-(ω-cyclohexyloxy)	32	----	S85
Docosyl	8	80	----	S38

R	n	%Yield	Remarks	References
Pentacosyl	10-(ω-cyclohexyl-oxy)	58	----	S85
(e)	XX	XX	----	115

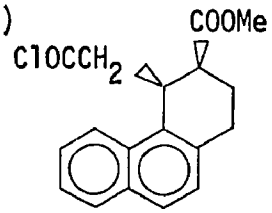
(a) ( ) shows substituents on main chain

(b) XX means unreported yields

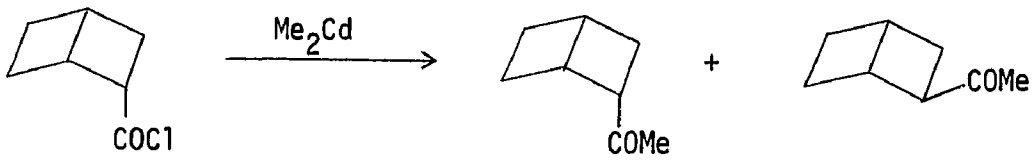
(c) "S" refers to literature citations in Shirley (4)

(d) 

(e) Made all 4-16-oxo-dodecyl esters; no yield, no experimental

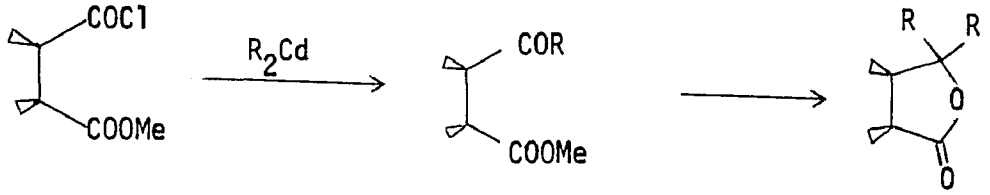
(f) 

starting acid chloride, but when the reaction was run with salt-free



Equation 42

dimethylcadmium similar results were obtained. It should be noted however, that after 40 days in a Dry-Ice acetone bath the mixture of the bicyclic products above was 51:49, endo:exo. Thus, perhaps the organocadmium compound reacted stereospecifically, and the resultant ketones then underwent isomerization. Indeed, this aurgument is supported by the work of Cason and Schmitz (109), who found no epimerization (Equation 43) in the lactone product from optically active compound (N) with organocadmium reagents. In the preparation



(N)

Equation 43

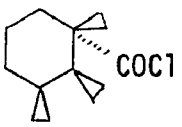
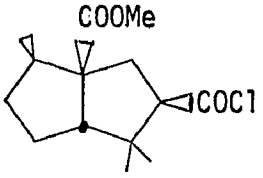
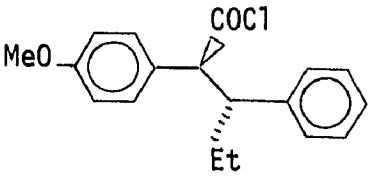
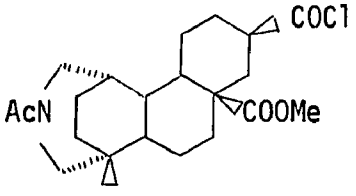
of the starting acid chloride-ester, however, some epimerization did take place and this amount was carried through into the lactone. Subsequently, other authors have found that no significant change in optical activity has been observed in the reaction of organocadmium reagents with asymmetric acid chlorides (see Table IV).

It is worthy of note that Lwowski (100) reacted optically active acid chloride-ester (O) with methylcadmium chloride and obtained two

TABLE IV

Reaction of Asymmetric Acid Halides[a] with Organocadmium Reagents

$$R^*COX + R_2Cd \longrightarrow R^*COR$$

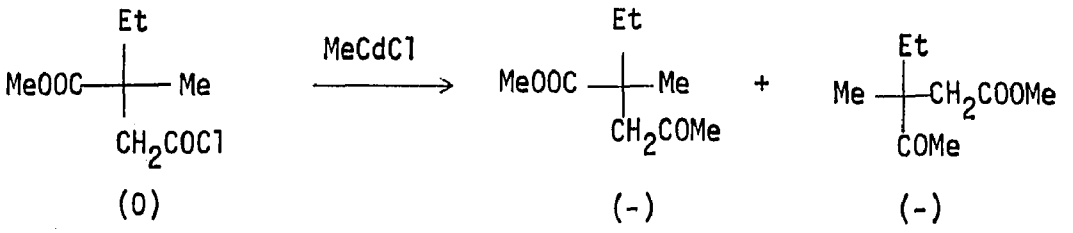
R	R*CHX[c]	%Yield	References
Me	$CH_3CH_2CH_2CH_2$ $\diagdown$ CHCOBr $\diagup$ CH_3CH_2	65	118
Me	CH_3 Ph — COCl H	50-70	119
Me		47	120
Me		XX[b]	120
Me		75%	122
Me		XX	123
n-Pr	Thebaine Derivative-COCl	80	124

(a) Cholesteryl Derivatives:Table VI

(b) Yields labelled XX were not given in literature

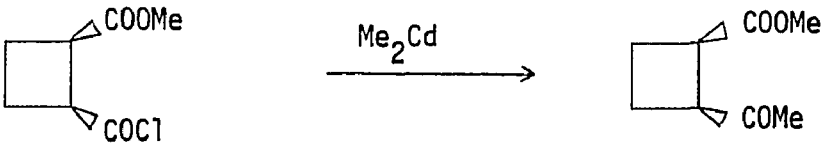
(c) * Denotes asymmetry

types of ketones in 46% yield through functional group exchange (Equation 44); the asymmetric center was exchanged, intact.



Equation 44

Compounds containing strained ring systems have been subjected to organocadmium reactions. As has been mentioned (Equation 42), when endo-2-chlorocarbonyl 2.2.0 -bicyclohexane reacted with dimethylcadmium, the product consisted of both endo- and exo- ketones. In contrast, cis-2-carbomethoxycyclobutane carbonyl chloride (99) reacted in 40% yield with dimethylcadmium. Here no isomerization was reported (Equation 45).



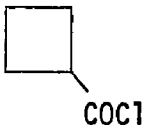
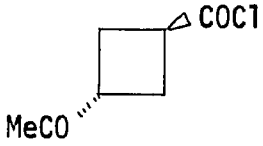
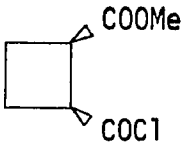
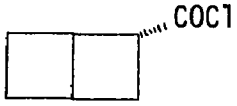
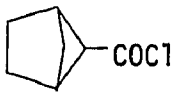
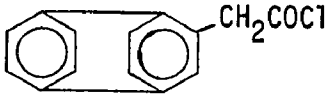
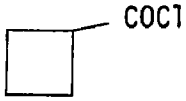
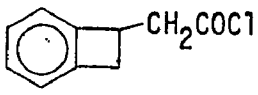
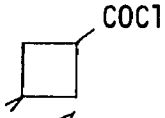
Equation 45

The following table lists various strained ring systems that have been subjected to organocadmium reagents. Some of the examples are, in addition, asymmetric or contain other functional groups and could have been placed in the appropriate tables. However, the ring functionality makes them unique and thus they are listed here.

Various unsaturated acid chlorides have been used as substrates in organocadmium reactions. Although cis-α,β-unsaturated compounds

TABLE V

Reactions of Organocadmium Compounds with Acid Chlorides Containing Bicyclic or Strained Rings

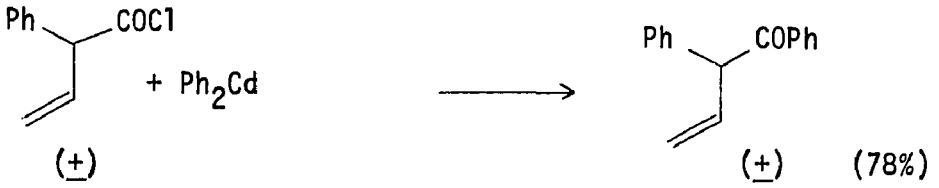
R	R'COCl	%Yield[b]	Remarks	References
Me		66	Diaddition to alcohol if reaction run at room temperature	S45
Me		74	----	125
Me		40	----	99
Me		51	endo and exo isolated	117
Me		88	----	126
Me		83	----	127
n-Pr		77	----	128
n-Pr		XX	----	50
i-Pent		XX,67	----	128
Ph		70	----	129

(a) "S" refers to D. A. Shirley (4)

(b) XX = no yield reported

have yet to be reported, many trans-isomers have been converted to products whose geometry has been preserved.

One substrate of note is (±)-vinylphenylacetyl chloride (Equation 46). The α-hydrogen is allylic, benzylic and α to a carbonyl,



Equation 46

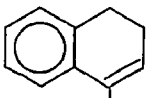
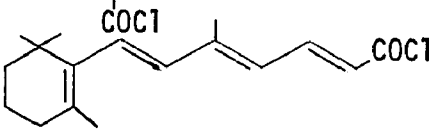
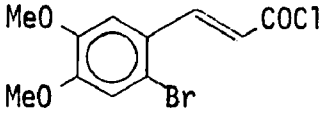
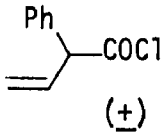
and yet no isomerization in the product was noted (130). This points up the possibility that cadmium reagents are not as basic as is generally thought (this property will be elaborated later).

Table VI lists the unsaturated compounds treated with organocadmium reagents. All starting materials have a trans configuration, where appropriate. As before, references preceded by "S" refer to citations from Shirley's review (4).

The formation of ketones from cholesteryl acid chlorides has been reported in many instances. The route from the organocadmium reagent is usually the method of choice because few side reactions are noted, such as diastereomeric isomerization, attack at ester protecting functions, or heteroring formation. The acid chlorides in Table VII are arranged for ease of reading. R" is the main steroid ring system; R' shows the substituents on the ring; and the side group construction is shown under the acid chloride heading. All but three entries have the acid chloride on the side chain. Entry #5 has the acid chloride in the 3-position, while entries #6 and #9 have steroid fragments.

TABLE VI

Reactions of Unsaturated Acid Chlorides with Organocadmium Reagents

R	R'COCl	%Yield[a]	Remarks	References
Me	$CH_3CH=CHCOCl$	55	----	19
Me		XX	----	S116
Me		45	----	131
Et	$CH_2=CHCH_2C(CH_3)_2COCl$	XX	----	132
Et		61	----	62
Et	$CH_3CH=CH=COCl$	35	react as EtCdCl	133
n-Pr	$CH_3CH=CHCOCl$	25	50% in Benzene	19
n-Pr	$(CH_3)_2C=CH-COCl$	XX	----	134
n-Bu	$CH_3CH=CHCOCl$	50	45% in Benzene	19
n-Bu	$(CH_3)_2C=CHCOCl$	XX	----	134
Ph	PhCH=CHCOCl	44	----	S123
Ph	 (±)	78	no rearrangement of double bond	130
n-Hept	$CH_2=CH(CH_2)_8COCl$	37	----	74
(b)	PhCH=CHCOCl	59	with $FeCl_3$ at room temperature	32
(b)	PhCH=CHCOCl	46	with $FeCl_3$ at 0^o	32

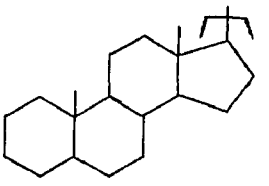
(a) XX=no reported yield

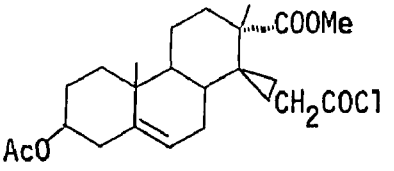
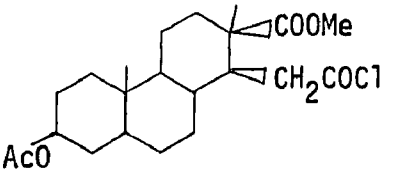
(b) no reported organic radical

TABLE VII

Synthesis of Ketones from Cholesteryl Derivatives by way of Organocadmium Reagents

$$\text{Cholesteryl-COCl} \xrightarrow{R_2Cd} \text{R'-COR}$$

R" = 

R	Acid Chloride	%Yield	Remarks	References
Me*	R'-COCl R'=3Keto,Δ^4R"	43	labelled Me^*_2Cd	135
Me	R'-COCl R'=3-AcOR"	92	crude yield	136
Me	R'-COCl R'=3-AcO,Δ^5R"	95	2.5 molar equivalents Me_2Cd	137
Me	R'-$CHCH_3$-COCl R'=3-AcO,Δ^5R"	75-95	----	S31
Me	R'COCl R'=17-C_8H_{17},3-COCl	82	----	S144
Me		54	----	138
Et	R'-$CHCH_3$COCl R'=β-AcO,Δ^4R"	93	----	S31
Et	R'-$CHCH_3$COCl R'=3-AcO,Δ^5R"	93	----	132
Et		66	----	139

R	Acid Chloride	%Yield	Remarks	References
i-Pr	R'-$CHCH_3(CH)_2COCl$ R'=3AcO,Δ^5R"	53	----	S49
i-Bu*	R'-$CH(CH_3)CH_2COCl$ R'=3AcO,Δ^5R"	71	radioactive $(CH_3)_2CH\overset{*}{C}H_2\rightarrow_2Cd$	36
i-Pent	R'$CH(CH_3)COCl$ R'=3AcO,Δ^5R"	91,95	----	S31
Ph	R'-$CH(CH_3)COCl$ R'=3AcO,Δ^5R"	81	----	137
Ph	R'COCl R'=3AcOR"	--	----	S51
Ph	R'$CH(CH_3)COCl$ R'=3AcOR"	--	----	S51
Ph	R'$CH(CH_3)COCl$ R'=3,12-AcO_2R"	--	----	S51
Ph	R'$CH(CH_3)COCl$ R'=3AcO,Δ^5R"	73	----	S31
Ph	R'$CH(CH_3)CH_2COCl$ R'=3AcOR"	--	----	S51
Ph	R'-$CH(CH_3)CH_2COCl$ R'=3AcO,R-keto-R'	--	----	S51
Ph	R'-$CH(CH_3)CH_2COCl$ R'=3,12-AcO_2,7-keto-R"	--	----	S51
Ph	R"-$CH(CH_3)CH_2COCl$	XX,75	----	S51,S145
Ph	R'-$CH(CH_3)CH_2COCl$ R'=3-AcO-R"	--	----	S51
Ph	R'-$CH(CH_3)CH_2COCl$ R'=3,12-AcO_2R"	64	----	S51
Ph	R'-$CH(CH_3)CH_2COCl$ R'=3,7,R-AcO_3-R"	--	----	S51

R	Acid Chloride	%Yield	Remarks	References
Mes	R'-Ch(CH_3)COCl R-=3AcO,Δ^5R"	--	----	S31
Mes	R'-CH(CH_3)COCl R'=3-AcO,Δ^5-R"	46	----	137

Reactions of acid anhydrides with organocadmium reagents have had limited use due partly to the low yields that have been reported and partly from side product formation.

De Benneville performed an extensive study on cadmium reactions of anhydrides. The best yields are obtained from diphenylcadmium and acyclic anhydrides (Equation 47). He also reported the yield of the

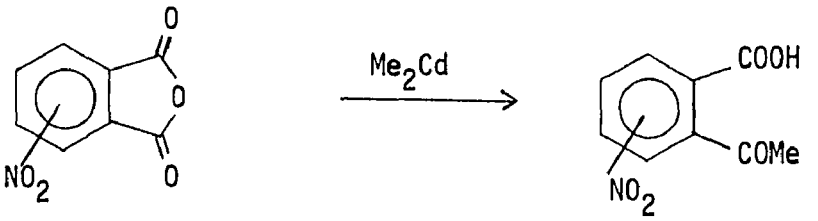
$$Ph_2Cd + (RCO)_2O \longrightarrow RCOPh$$

R	%Yield
CH_3	75
Et	68
i-Pr	72

Equation 47

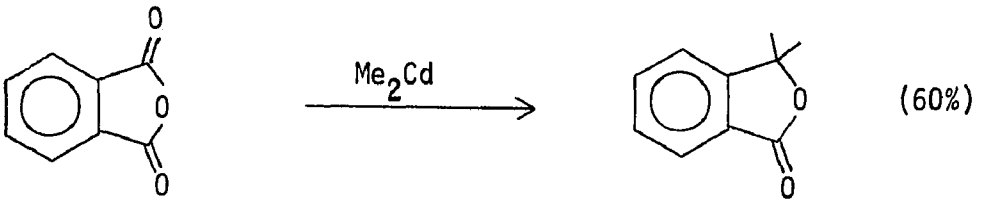
reaction between dimethylcadmium and phthalic anhydride to be 47-63% of the o-acetylbenzoic acid.

3- and 4-nitrophthalic anhydrides react with dimethylcadmium (41) to give the keto acids in 30 and 38%, respectively (Equation 48).



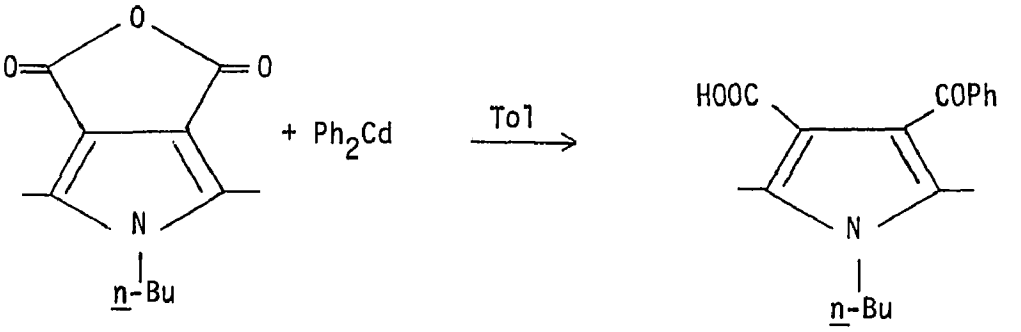
Equation 48

In contrast to De Benneville's report, these authors found that reaction of dimethylcadmium with phthalic anhydride does not give the keto acid but instead 3,3-dimethylphthalide (Equation 49). Both of these groups used identical reaction conditions in their work; addition of the anhydride in ether at ice-bath temperatures, refluxing for 1-2 hr, and 10% H_2SO_4 work-up.



Equation 49

An anhydride derivative of pyrrole has been allowed to react with diphenylcadmium to give the keto-acid derivative (Equation 50).



Equation 50

Anhydride reactions are listed in Table VIII.

Rearrangements

The rearrangements of organocadmium reagents are not well-known. Indeed, most reviews dealing with the subject of organometallic rearrangements contain no mention of cadmium reagents.

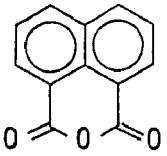
However, it has been shown (147) that reactions of dicrotylcadmium with ketones and aldehydes lead exclusively to rearranged alcohols (Equation 51). It has also been reported (148) that dicrotylcadmium, when hydrolyzed with water, gives 1-butene as the main product.

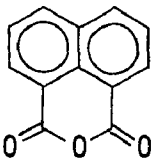
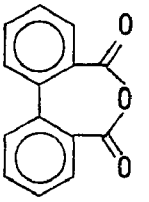
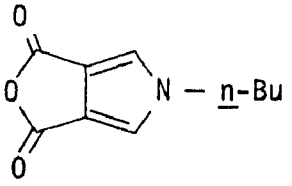
TABLE VIII

The Reactions of Anhydrides

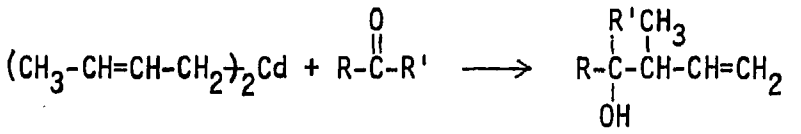
with Organocadmium Reagents

$$(R'CO)_2O + R_2Cd \longrightarrow RCOR'$$

R	$(R'CO)_2O$	%Yield[a]	Remarks	References
Me	Phthalic	47-62	yield depended on MeX X=I,Br	40
Me	Phthalic	0	60% phthalide	141
Me	Phthalic	XX	----	98
Me	3-Nitrophthalic	53	----	143
Me	3-Nitrophthalic	29.7	----	141
Me	4-Nitrophthalic	40	also phthalide	144
Me	4-Nitrophthalic	38	----	141
Me	4-Acetamidophthalic	6.7	22% phthalide	141
Et	Phthalic	64-67	3 Mol. eq. Me_2Cd	140
Et	PhCOOCOOEt	0	61% PhCOEt	145
Et		95	----	42
Et	Benzoic	53	----	140
i-Pr	Benzoic	33-44	as i-PrCdBr i-PrCdI	140
n-Bu	Acetic	56	trace without magnesium salts	25
n-Bu	Acetic	55	55% when reconstituted	26
t-Bu	Benzoic	40	----	140

R	$R'CO)_2O$	%Yield	Remarks	References
Ph	Acetic	75	----	140
Ph	Propionic	68	----	140
Ph	Succinic	30	----	140
Ph	Isobutyric	72	----	140
Ph	3-Nitrophthalic	53	----	143
Ph	4-Nitrophthalic	29	----	144
Ph		57	95% from Grignard	42
Ph		87	----	42
Ph		10	----	142
1-Naphthyl	Phthalic	47-62	----	140

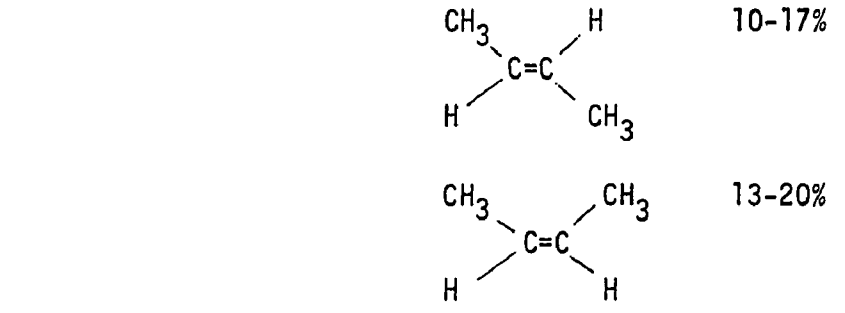
(a) XX means no reported yield



R	R'
tert-Bu	H
n-Bu	H
Ph	H
Me	Et
Et	Et

Equation 51

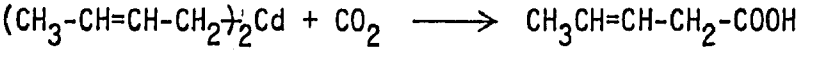
Interestingly, the other products obtained were the expected trans-2-butene and cis-2-butene (Equation 52).



Equation 52

The fact that cis- and trans- isomers show up in essentially equal yields may indicate that the crotylcadmium and 1-butenylcadmium reagents are in equilibrium.

In contrast, "salt-free" dicrotylcadmium (149), prepared from the corresponding boron reagent, reacts with carbon dioxide to give the unrearranged acid (Equation 53).



Equation 53

Unlike the corresponding Grignard reagent, dibenzylcadmium does not rearrange to give ring substitution with either acid chlorides or carbonyl compounds (150).

As has already been mentioned in the Introduction, three groups of workers have found the m-dianisylcadmium reagent leads to rearranged (para) products with aromatic and aliphatic chlorides and with aliphatic acid anhydrides. Dauben and Collette (2) in addition showed that o-, m-, and p-ditolylcadmium reagents give no appreciable rearrangement. In the case of o-dianisylcadmium reacting with acetyl chloride, 4% of the total isolated yield was found to be p-methoxyacetophenone. Analysis of the starting material showed only 0.5% of p-bromoanisole. Thus, formation of some of the para products must be attributed to rearrangement. Although no explanation was presented for this side product, it is thought that the internal Lewis acid ability of the cadmium atom may cause a small but significant amount of methylcarboxonium ion to be produced. This was then attacked in the manner of a Friedel-Crafts reaction by anisole.

The problem of the rearrangement of arylcadmium reagents is the subject of Part I of this thesis.

EXPERIMENTAL

Infrared (ir) spectra were recorded as films or KBr pellets on a Perkin-Elmer Model 337 grating spectrophotometer. Nuclear Magnetic Resonance (nmr) spectra were recorded on a Jeol JMN-MH-100 spectrometer in deuteriochloroform, unless otherwise noted. Chemical shifts are reported in parts per million downfield from tetramethyl silane as an internal standard. All spectra were compared to those reproduced by Sadtler Laboratories (151) where appropriate.

Gas liquid partition chromatographic (glpc) analyses and separations were performed with a Varian Model 90-P Gas Chromatograph equipped with a 10' X ¼" copper column packed with 10% carbowax 2M on chromosorb W. Column conditions are noted where appropriate. Collection of samples from the gc for ir analyses was accomplished by employing a V-shaped glass tube at the gas exit with the bend submerged in a Dry Ice-acetone bath. A number of runs were usually necessary to collect sufficient sample for analysis. The contents of the tube were washed with ether directly onto salt plates, or onto KBr, and the solvent removed by evaporation. Collection of samples for nmr analyses usually required a larger number of runs. This was accomplished by placing an L-shaped tube directly into an nmr tube which was placed in an ice-water bath.

Peak areas were determined as the product of the height and the half-height peak width. Exact ratios of peaks was determined using internal standards.

Melting Points (mp) were determined on a Hoover Capillary Melting Point Apparatus and are uncorrected. All temperatures are

reported in degrees Centigrade. Elemental analyses were performed either at Galbraith Laboratories, Knoxville, Tennessee, or by Mrs. Judy Daigle of UNH.

The materials used in the reactions were either obtained commercially or synthesized independently. Diethyl ether was refluxed and distilled from lithium tetrahydridoaluminate and stored over sodium wire. Acetyl chloride was obtained from Allied Chemical Co. and distilled prior to use. Cadmium chloride was heated in an oven at 125° for at least 48 hr prior to use.

m-Bromoanisole was obtained from Aldrich Chemical Co and vacuum distilled prior to use, because glpc analysis showed that it contained a large amount of m-bromoaniline (UNH ir:23155) which was saved and used in subsequent reactions.

UNH ir:	23154
Sadtler ir:	42441
Sadtler nmr:	13769

m-Bromonitrobenzene. This procedure is essentially that of Johnson and Gauerke (152). A 3-necked, 250-mL round-bottomed flask, fitted with an addition funnel, condenser and thermometer, and containing 90 g (0.732 mol) of freshly distilled nitrobenzene, was heated with magnetic stirring to 135-145° in an oil bath. Then 2.5 g of iron filings (40 mesh) was added. A hose was attached to the top of the condenser and run to a position above the surface of some water contained in a beaker. This was to monitor the evolution of HBr and Br_2 that might have passed through the condenser. Twenty mL of bromine was added dropwise over a period of 30 min to the rapidly stirred mixture such that little or no bromine traversed the condenser. Heating was continued for an additional 30 min after the addition. At this time another 2.5 g of iron filings

was added and another 20 mL of bromine was added dropwise. Again the mixture was heated for 60 min after addition. This process was repeated once more. At that time 1.2 g of iron filings was added and heating continued for 60 min. After being cooled to room temperature, the mixture was quenched with 500 mL of water containing 16 mL of saturated sodium sulfite. The product was collected by steam distillation as a pale yellow solid in a beaker of ice water. This was done in a hood because sulfur dioxide was evolved. When no more solid was being collected, the crude product was isolated by suction filtration. The solid was vacuum distilled to afford 69.7 g (47%) of pale yellow crystals, bp 95-110° (1.5 mm); mp 50-53°; lit[153] mp 56°.

UNH ir: 22946
Sadtler ir: 16554

m-Bromoaniline. This process is essentially that of Speekman and Wilbault (154). To a 3-necked, 500-mL round-bottomed flask, fitted with a condenser and a gas inlet tube, were added 50 g (0.248 mol) of m-bromonitrobenzene, 50 g of iron filings (40 mesh) and 250 mL of 95% ethanol. The inlet tube was placed well below the surface of the ethanol. The other end of this tube was connected via a calcium chloride drying tube to the side arm of a filter flask containing sodium chloride. Concentrated sulfuric acid, contained in a separatory funnel that was placed into the flask via a one-holed rubber stopper, was dripped onto the salt so as to generate HCl at such a rate that a vigorous reaction was maintained in the round-bottomed flask. Heating the filter flask was necessary to generate a steady stream of dry HCl. The HCl generator was emptied and recharged when spent. After about 2 hr, when no more refluxing took place, the mixture was heated for an additional 60 min.

The apparatus was then changed over to a distillation set-up, and 150 mL of ethanol was collected. After 250 mL of water had been added, the mixture was distilled until the temperature of the distillate reached 90°. The residue was made alkaline and the milky suspension steam distilled. When no more immiscible amine came over, the oil was separated and the aqueous layer was extracted twice with 100 mL of ether. The extracts and oil were dried (Na_2SO_4) and concentrated in vacuo. The oily residue was then vacuum distilled to afford 19.3 g (45%), bp 90-95° (0.5 mm); lit[155] bp 122-124° (10 mm).

m-Bromo-N,N-dimethylaniline. This procedure is essentially that of Sheppard (156). A 3-necked, 250-mL round-bottomed flask, with a reflux condenser, addition funnel and thermometer, and containing 17.2 g (0.10 mol) of m-bromoaniline and 14.3 g (0.102 mol) of trimethyl phosphate, was heated with magnetic stirring to 150° over a period of 60 min in an oil bath under a nitrogen atmosphere. The flask was cooled and 15 g of sodium hydroxide in 100 mL of water was added with rapid stirring. The mixture gelled and stirring became impossible. A stirring rod was used to break the gel so that stirring could be continued. After 90 min, 200 mL of water was added, and the cooled solution was extracted twice with 150 mL of ether. The ether was dried ($MgSO_4$) and concentrated under vacuum. When the residual oil was vacuum distilled, there was obtained 12.5 g (63%) of colorless oil, bp 65-70° (0.05 mm); lit[157] bp 133-134° (15 mm).

UNH ir: 22970
Sadtler ir: 24368 (m-chloro compound used for comparison)

m-Bromofluorobenzene. This procedure is essentially that of Flood (157). To a 3-necked, round-bottomed flask, fitted with a mechanical stirrer,

addition funnel and a thermometer containing 25 mL of water, 16.5 mL of concentrated HCl, and 11.0 g (0.050 mol) of m-bromoaniline, maintained at 5^{o} in a Dry Ice-acetone bath was added slowly an ice-cold solution of 12.0 g of sodium nitrite in 25 mL of water. The internal temperature was never allowed to exceed 7^{o}. At the same time 22.0 g (0.10 mol) of additional aniline was added, such that all had been introduced before one-half of the nitrite solution was added. After the remainder of nitrite had been added, 30 g (0.34 mol) of ice-cold fluoboric acid (J. T. Baker) was added at a fairly rapid rate, the temperature being maintained below 10^{o}. After the orange mixture had been stirred for another 30 min, the solid was collected by suction filtration. The precipitate was washed with 15 mL of cold water, 15 mL of cold methanol, and 15 mL of cold ether, being dried as thoroughly as possible between washings, and then placed in a vacuum desiccator overnight. The pink crystals were placed in a 500-mL, round-bottomed flask, fitted with a good condenser (in a good hood, since BF_3 was to be generated in the next step). The flask was heated with a flame near the top of the solid. Although the decomposition was supposed to proceed spontaneously, repeated heatings were necessary to complete the conversion. Finally the contents of the flask were heated vigorously. The reflux set-up was converted for distillation, and m-bromofluorobenzene was distilled by means of a Bunsen burner. The oily distillate was then washed twice with equal volumes of 15% NaOH and water, and dried ($CaCl_2$), decanted and distilled to give 8.2 g (29%); bp 152^{o}, lit[158] bp $84-85^{o}$. In a second run with a more efficient reflux condenser, the yield was 45%.

UNH ir: 23473
Sadtler ir: 18939

m-Bromotrifluoromethylbenzene. This procedure is described by Simons and Ramler (159). A 3-necked, 1-L round-bottomed flask, fitted with a mechanical stirrer, addition funnel, condenser and thermometer, and containing 133 g (0.91 mol) of trifluoromethylbenzene (Aldrich) and 1 g of iron filings (40 mesh), was heated to 60° on a steam bath, whereupon 3 mL of bromine was added dropwise. If the reaction failed to start (identified by loss of bromine color and spontaneous refluxing) the temperature was increased to 70° and another gram of iron was added. Once the reaction had started, 21 mL of bromine was added dropwise over a period of 1 hr. Heating and stirring were continued for 1 hr, at which time another 25 mL of bromine was added. After being stirred for an additional hour, the mixture was cooled and poured into a solution of 700 mL of water and 25 mL of saturated sodium sulfite. More solid Na_2SO_3 was added until all the red color had dissipated. The mixture was then steam distilled until no more oily compound was collected. The separated oily layer was washed with dilute KOH, dried ($MgSO_4$) and distilled at atmospheric pressure through a Vigreaux column to give 86.1 g (42%) of a colorless liquid; bp 149-155°; lit[159] bp 156°.

UNH ir: 23474
Sadtler ir: 20109

Ethyl Potassium Xanthate. A 3-necked, 250-mL round-bottomed flask, fitted with an addition funnel, mechanical stirrer and thermometer, and containing 40 mL of absolute ethanol (Rossville, Gold Shield) and 5.6 g (0.10 mol) of KOH, was heated on a steam bath with stirring until the KOH was dissolved. While the temperature was maintained between 40-50°, 8.2 mL (10.3 g, 0.14 mol) of carbon disulfide was added dropwise in 10 min. The flask was then cooled and 100 mL of petroleum ether was

added. The solid sludge, after being broken up with a stirring rod, was collected by suction and the precipitate was washed with petroleum ether until the washings were colorless. The solid, dried by suction for 30 min, was used without further purification: crude yield 17.2 g (106%).

Ethyl m- Bromophenyl Xanthate. This procedure is essentially that of Tarbell and Fukushima (160). A 3-necked, 250-mL round-bottomed flask, fitted with a mechanical stirrer, addition funnel and low temperature thermometer and containing 20 g of crushed ice and 18.7 g of concentrated HCl was cooled in an ice-salt bath, while 17.2 g (0.10 mol) of m-bromoaniline was added slowly. When the temperature reached 0^{o}, a cold solution of 6.9 g (0.10 mol) of sodium nitrite in 15.6 mL H_2O was added slowly, the temperature being held below 4^{o}. This orange solution was kept cold during the addition to the xanthate which was to follow.

A 3-necked, 500-mL round-bottomed flask fitted with a mechanical stirrer, addition funnel and thermometer, and containing 17.0 g (0.11 mol) of ethyl potassium xanthate in 22.5 mL of water was stirred and heated on a steam bath to 70^{o}. The cold diazonium solution was added dropwise from an addition funnel in 15-mL portions, the remainder being kept cold in an ice-salt bath. CAUTION: EXPLOSIONS HAVE BEEN REPORTED AT THIS STAGE (160). When all the diazonium salt had been added, (approx. 45 min), the solution was stirred at 70^{o} for 1 hr and then cooled to room temperature. The red oil was separated and the aqueous layer was extracted twice with 50 mL of ether. The extracts were combined with the oil and the ether was evaporated on a steam bath under a stream of nitrogen in a good hood. The xanthate was used without

further purification.

m-Bromothiophenol. This procedure is essentially that of Bordwell and Anderson (161). To a 3-necked, 500-mL round-bottomed flask, fitted with a mechanical stirrer and reflux condenser and containing 16 g of KOH in 100 mL of methanol and 16 mL of water, was added the oil from the preceding step, and the contents were heated at reflux under nitrogen for 2 hr. This solution was then added, with stirring, to a 2-L flask containing 1 L of water. The mixture was acidified to Congo red paper with concentrated HCl. The oil was separated and the aqueous layer was extracted twice with 50 mL of methylene chloride. The extracts and oil were combined and evaporated on a steam bath under a stream of nitrogen to constant weight. The resulting oil was used without further purification.

m-Bromophenyl Methyl Sulfide. To a solution of the oil obtained above in 11.7 g of NaOH and 147 mL of methanol, was added 8.8 mL of dimethyl sulfate. The mixture was heated under reflux with magnetic stirring for 1.5 hr, was cooled to room temperature and then extracted with 100 mL of methylene chloride. The gel that formed was acidified (pH paper) with 10% HCl. The organic layer was separated, washed with 50 mL of 10% ammonium hydroxide, 50 mL of 5% $NaHCO_3$ and 50 mL of H_2O, dried ($MgSO_4$) and concentrated under a stream of nitrogen. Vacuum distillation yielded three fractions boiling over a range of 65-73° (0.5 mm), all having identical irs, giving 7.5 g (36.9% yield, based on m-bromoaniline); lit[161] bp 100-104° (10 mm).

UNH ir: 23336, 23337, 23338
Sadtler ir: 21710

Preparation of p,p'-Bianisyl. A solution of 50 g (0.03 mol) of p,p'-dihydroxybiphenyl and 4.0 g (0.01 mol) of sodium hydroxide in 50 mL of methanol was magnetically stirred as 4.0 g of dimethyl sulfate was added dropwise. After refluxing for 60 min, the mixture was cooled, and the solid was collected by suction filtration and recrystallized from 95% ethanol; mp 174-176°; lit[162] mp 174°. The filtrate was rotary evaporated, dissolved in ether and washed with 5% NaOH. The ether layer was dried (Na_2SO_4) and concentrated in vacuo. Recrystallization of this solid from 95% ethanol gave a second crop of solid; mp 175-177°. The total yield was 3.8 g (90%).

UNH ir:	23381
Sadtler ir:	37791
UNH nmr:	7203
Sadtler nmr:	8099

Phenyl Cyanate. This procedure is essentially that of Grigat and Putter (163). A 3-necked, 250-mL round-bottomed flask, fitted with a mechanical stirrer, addition funnel and low-temperature thermometer, and containing 5.4 g (0.05 mol) of cyanogen bromide (Aldrich) in 100 mL of dry ether, was cooled to -10° (or lower) in a Dry Ice-acetone bath and maintained there throughout the reaction. A solution of 4.65 g (0.05 mol) of phenol (Mallinckrodt) and 5.0 g (0.05 mol) of triethylamine in 50 mL of dry ether was added to the rapidly stirred solution over a period of at least 15 min. After being stirred an additional 20 min, the precipitate was collected by suction filtration and washed with 50 mL of ether. The filtrate was then washed with 5% NaOH, dried ($MgSO_4$) and concentrated in vacuo. Vacuum distillation of the residual oil yielded 3.6 g (30%); bp 40-45° (0.5 mm); lit[163] bp 82-83° (17 mm).

Diacetyl Sulfide. Into a flame-dried, 100-mL round-bottomed flask fitted with a reflux condenser topped by a $CaCl_2$ tube was added 10.5 g (0.14 mol) of thiolacetic acid (Aldrich) and 21.6 g (0.28 mol) of acetyl chloride. The mixture started to heat up immediately. After the initial reaction slowed, the flask was heated gently for 4.0 hr. The contents of the flask were then vacuum distilled (CAUTION: stench) at an aspirator. Three fractions were collected; $<51^{\circ}$, 51-58° and 58-61°. The infrared spectra of the latter two fractions (23319, 23320) were identical to the Sadtler spectrum (45787); lit[164] bp 58-59°. The combined fractions amounted to 9.3 g (66%).

Titration of n-Butyllithium. This procedure was reported by Watson and Eastham (165). A one-molar solution of sec-butyl alcohol in dry xylene was prepared and placed into a buret equipped with a syringe needle at the bottom. Into a 3-necked, 100-mL round-bottomed flask was placed 10 mg of 2,2'-bisquinoline. The flask was flame dried and capped with rubber septa. A stream of nitrogen was introduced through one septum and allowed to exit through another. The buret was connected to the middle septum. A 10-mL aliquot of n-butyllithium (Ventron) was placed in the flask via syringe and the nitrogen inlet was removed. The magnetically stirred solution (red) was then titrated with the alcohol solution to a slightly yellow endpoint, 23.0 mL of the alcohol being required; thus the 2.40 M n-butyllithium was in fact 2.3 M.

Acetylation of Anisole with Magnesium Chloride and Cadmium Chloride as Lewis Acids: A Control Experiment. Into each of four one-necked, 100-mL round-bottomed flasks was placed 2.2 g (0.02 mol) of anisole in 50 mL of dry ether. All were stirred magnetically, as 1.56 g (0.02 mol) of acetyl chloride was added. Flask one was charged with 1.83 g

(0.01 mol) of cadmium chloride; flask two- 1.88 g (0.02 mol) of magnesium chloride, flask three - 1.83 g $CdCl_2$ and 1.88 g $MgCl_2$; and flask four - none of these salts. They were each topped with a $CaCl_2$ drying tube and the contents stirred overnight. In the morning each was acidic to pH paper. Water was added and stirring continued for 0.5 hr. The layers were separated and the aqueous layer was extracted with ether. The combined ether portions were washed with 5% $NaCO_3$, dried over $NaSO_4$ and rotary evaporated. There was no evidence of carbonyl compounds present in any of the four samples as judged by gas chromatography.

Gc Conditions:	Column Temp:	149^o
	Detector Temp:	198^o
	Gas Flow:	65 ml/min
	Sample sizes:	1 μL

General Procedure for Organocadmium Reactions. The general procedure for preparing and using organocadmium reagents was as follows. To a 3-necked, round-bottomed flask, fitted with a mechanical stirrer, addition funnel and reflux condenser, was added magnesium (either turnings from J. T. Baker or triply-sublimed magnesium from Dow Chemical Co.; both seemed to exhibit similar reactivity). Nitrogen was allowed to flow through the system through the top of the addition funnel and out from the top of the condenser to an oil bubbler which served as a flow regulator. The system was flamed dried with the condenser turned off and then cooled to room temperature. With the condenser then turned on, one-half the bromo compound in ether was allowed to drip in, and stirring was started. The nitrogen was slowed to about 1-2 bubbles per sec. When the reaction started, the rest of the bromo compound was added dropwise as rapidly as possible. The cadmium chloride was added in one portion to the Grignard reagent by increasing the nitrogen flow,

disconnecting the reflux condenser and adding the salt directly to the flask. The condenser was replaced, the nitrogen slowed, and the reaction mixture stirred until a Gilman test showed the absence of any Grignard (166). The cadmium reagent was cooled and the next reagent was added dropwise as an ethereal solution. Work-up consisted of hydrolysis in the flask with 10% HCl, stirring for 30 min or longer, separating the ether layer, washing the aqueous layer once with ether, washing the combined ether portions with 5% $NaHCO_3$, saturated brine, drying over $MgSO_4$ or $NaSO_4$, and rotary evaporating the solution to give crude products. Specific details are given in the appropriate sections. No attempt was made to maximize the yields.

Standardization and Analysis of m- and p-methoxyacetophenones by Gas Chromatography. Yields and product ratios were determined by weighing three authentic samples of meta-methoxyacetophenone (Aldrich) and adding known amounts of biphenyl. These samples were mixed with some ether, injected into the gas chromatograph and the peak areas were measured (height X width at half-height). The ratios of the peaks (meta-methoxyacetophenone/biphenyl) were plotted against the ratios of the known weights. Since straight lines resulted, a factor was determined by which ratios of peaks from unknown samples could be multiplied to give the true ratios. para-Methoxyacetophenone was standardized in a similar manner. When an unknown sample was to be determined, some of the sample was weighed out into three vials and a weighed amount of biphenyl was added. These were mixed with some ether and injected into the gas chromatograph. The peak areas were determined for the meta and para compounds and for the biphenyl. The

meta to biphenyl ratio was multiplied by the "meta" factor and the para to biphenyl ratio was multiplied by the "para" factor. These were then multiplied by the weight of biphenyl used in that particular sample giving the true weights of meta and para ketones. The weight of meta and para are added together and divided by the weight of the crude oil used in the sample to give the % of the sample that contained ketonic products. This percent is then multiplied by the total weight of the reaction yield to give the true product yield of ketone. This can then be divided by the theoretical yield to give the true percent yield. An example is given below:

		1	2	3
A.	Weight of unknown (g):	0.1189	0.0965	0.1607
B.	Weight of biphenyl (g):	0.0103	0.0086	0.0101
C.	Peak area of biphenyl:	9.08	8.58	7.94
D.	Peak area of m-MeOPhAc:	14.95	12.43	15.30
E.	Peak area of p-MeOPhAc:	29.52	26.41	31.78
F.	Ratio of m- to biphenyl: (D/C)	1.646	1.449	1.927
G.	Ratio of p- to biphenyl: (E/C)	3.251	3.078	4.003
H.	Corrected Ratio of m- to biphenyl; (F x "meta" factor-0.9358):	1.540	1.356	1.803
I.	Corrected ratio of para to biphenyl; (G x "para" factor-1.1904):	3.870	3.664	4.764
J.	True weight of meta- isomer (g): (H x B)	0.0159	0.0112	0.0184
K.	True weight of para- isomer (g): (I x B)	0.0399	0.0315	0.0486

		1	2	3
L.	Total of ketonic products (g): (J + K)	0.0558	0.0427	0.0670
M.	% of crude oil containing ketonic products: (L/A x 100)	46.9	44.7	41.7
N.	Weight of crude oil containing ketonic products (g): ((M x product yield) ÷ 100)		1.29	
O.	Theoretical yield:		3.53	
	Actual yield: (N/O)		36.5	
	% meta-methoxyacetophenone: (J/L)	28.5	27.0	27.5
	% para-methoxyacetophenone:	71.5	73.0	72.5
	Average % m- ± avg. deviation:		27.7 ± 0.8	
	Average % p- ± avg. deviation:		72.3 ± 0.8	

The Reaction of m-Dianisylcadmium with Acetyl Chloride. To the Grignard reagent prepared from 0.60 g (0.025 mol) magnesium (Dow) and 4.68 g (0.025 mol) of m-bromoanisole in a total of 35 mL of dry ether, which was refluxed for 30 min and stirred at room temperature for 90 min, was added 2.29 g (0.013 mol) of cadmium chloride. The mixture was stirred at room temperature for 30 min and a solution of 1.96 g (0.025 mol) of acetyl chloride in 15 mL of dry ether was added dropwise to the cooled (cold water) organocadmium reagent. The mixture was heated at reflux for 30 min and stirred at room temperature for 12 hr. The usual work-up gave 2.90 g of crude oil. Gas chromatographic analysis showed both meta and para-methoxyacetophenone, identified by peak enhancement with authentic samples and infrared analyses of collected samples.

GC Conditions: Column temp: 151°
Detector temp: 200°
Flow rate: 65 mm/min
Injection sizes: 1-4 μL

Retention Times: Meta-: 17.0 min
Para-: 25.5 min

Yield Data: Product yield: 36.5%
% Meta-: 27.7 ± 0.8
% Para-: 72.3 ± 0.8

In a second reaction the result were as follows:

Product yield: 31.3%
% Meta-: 22.9 ± 1.7
% Para-: 77.1 ± 1.7

	m	p
UNH ir:	23040	23041
Sadtler ir:	20309	3883

The Reaction of m-Dianisylcadmium with Acetyl Bromide. To the Grignard reagent prepared from 0.60 g (0.025 mol) of magnesium (Dow) and 4.68 g (0.025 mol) of m-bromoanisole in a total of 50 mL of dry ether, which was refluxed for 60 min and stirred at room temperature for 60 min, was added 2.30 g (0.013 mol) of cadmium chloride. After the organocadmium reagent had been stirred at room temperature for 30 min, 2.00 g (0.016 mol) of acetyl bromide in 50 mL of dry ether was added dropwise. This mixture was stirred for 90 min, and the usual work-up gave 2.9 g of crude oil. Gas chromatographic analysis showed the presence of both m- and p-methoxyacetophenones. Column conditions were the same as those in the previous experiment.

Yield data: Product Yield: 28.8%
% Meta-: 25.4 ± 0.8
% Para-: 74.6 ± 0.8

The following data were obtained from a second reaction:

Product Yield:	18.0%
% Meta-:	23.0 ± 0.3
% Para-:	77.0 ± 0.3

The Reaction of Dianisylcadmium with Acetic Anhydride. To the Grignard reagent prepared from 0.60 g (0.025 mol) of magnesium (Baker) and 4.68 g (0.025 mol) of m-bromoanisole in a total of 50 mL of dry ether, which was refluxed for 30 min and stirred at room temperature for 60 min was added 2.30 g (0.013 mol) of cadmium chloride. The grey organocadmium reagent was stirred at room temperature for 30 min and 3.00 g (0.025 mol) of acetic anhydride (Baker) in a 25 mL of dry ether was added dropwise. When the orange mixture was hydrolysed with 10% HCl, an orange-red solution resulted. In a separatory funnel 3 layers were formed. The lower (aqueous) layer was drawn off. The intermediate, dark-orange, layer was found to be insoluble in ether, water and 5% HCl, but soluble in chloroform. When the upper orange layer was washed with bicarbonate it turned yellow. The second layer was dried and evaporated to give a dark orange solid, which is as yet unidentified. The rest of the work-up procedure on the upper layer gave 2.7 g of crude oil. Gas chromatographic analysis (conditions as above) showed the presence of both m- and p-methoxyacetophenone.

Product Yield:	18.9%
% Meta-:	74.7 ± 1.8
% Para-:	25.3 ± 1.8

The Reaction of m-Dianisylcadmium with Diacetyl Sulfide. To the Grignard reagent prepared from 0.24 g (0.010 mol) of magnesium (Baker) and 1.86 g (0.010 mol) of m-bromoanisole in a total of 30 mL of dry ether, which was refluxed for 15 min and stirred at room temperature for 30 min, was added 0.092 g (0.005 mol) of cadmium chloride. The

organocadmium reagent was stirred at room temperature for 30 min, when 1.18 g (0.010 mol) of diacetyl sulfide in 30 mL of dry ether was added dropwise. The mixture was stirred at room temperature for 60 min. The usual work-up gave 1.87 g of crude oil. Gas chromatographic analysis (conditions as above) showed the presence of only m-methoxyacetophenone, identified by peak enhancement.

Product Yield: 17.5%

In a second reaction, similar to that just described (except the Grignard reagent was refluxed for 90 min and the mixture, after addition of diacetyl sulfide, was refluxed for 2 hr) the meta isomer was formed in 31.2% yield, as the only ketone product.

The Reaction of m-Dianisylcadmium with Acetyl Chloride after the Precipitation of Magnesium Salts with Dioxane. To the Grignard reagent prepared from 0.60 g (0.025 mol) of magnesium (Baker) and 4.68 g (0.025 mol) of m-bromoanisole in a total of 45 mL of dry ether, which was refluxed for 60 min and stirred at room temperature for 30 min, was added 2.30 g (0.013 mol) of cadmium chloride. After the cadmium reagent had been refluxed for 60 min and then cooled, 4.40 g (4.20 mL, 0.050 mol) of dioxane was added dropwise. A fine white powder formed immediately. A solution of 2.00 g (0.025 mol) of acetyl chloride in 35 mL of dry ether was added dropwise and the mixture stirred at room temperature for 90 min. The usual work-up gave 3.75 g of crude oil. Gas chromatographic analysis (conditions as above) of this oil showed the presence of both m- and p-methoxyacetophenone.

Product Yield:	37.2%
% Meta-:	38.2 ± 1.3
% Para-:	61.9 ± 1.3

The Reaction of m-Anisylcadmium Chloride with Acetyl Chloride. To the Grignard reagent prepared from 0.60 g (0.025 mol) of magnesium (Baker) and 4.68 g (0.025 mol) of m-bromoanisole in a total of 50 mL of dry ether, which was refluxed for 60 min, was added 4.60 g (0.025 mol) of cadmium chloride. A solution of 2.00 g (0.025 mol) of acetyl chloride in 25 mL of dry ether was added dropwise and the mixture was stirred for 30 min at room temperature. The usual work-up gave 3.50 g of crude oil, containing both meta- and para-methoxyacetophenone.

Product Yield:	40.8%
% Meta-:	24.6 ± 1.1
% Para-:	75.4 ± 1.1

The Reaction of m-Anisylcadmium Bromide with Acetyl Chloride. To the Grignard reagent prepared from 0.24 g (0.010 mol) of magnesium (Dow) and 1.87 g (0.010 mol) of m-bromoanisole in a total of 25 mL of dry ether, which was refluxed for 15 min and stirred at room temperature for 30 min, was added 2.73 g (0.010 mol) of cadmium bromide, which had been heated in an oven at 125^{o} for 48 hr. After the cadmium reagent was refluxed for 30 min and stirred at room temperature for 90 min, 0.78 (0.010 mol) of acetyl chloride in 25 mL of dry ether was added dropwise with stirring to the mixture. The orange mixture was refluxed for an additional 30 min and cooled. The usual work-up gave 1.40 g of crude oil. Gas chromatographic analysis (conditions as above) showed the presence of both m- and p-methoxyacetophenone.

Product Yield:	24.6%
% Meta-:	24.0 ± 1.0
% Para-:	76.0 ± 1.0

The Reaction of m-Anisylcadmium Bromide with Acetyl Bromide. To the Grignard reagent prepared from 0.24 g (0.010 mol) of magnesium (Baker)

and 1.87 g (0.010 mol) of m-bromoanisole in a total of 25 mL of dry ether, which was refluxed for 30 min and stirred at room temperature for 30 min, was added 2.73 g (0.010 mol) of cadmium bromide. The organocadmium reagent was stirred at room temperature for 60 min, when 1.23 g (0.010 mol) of acetyl bromide in 25 mL of dry ether was added dropwise. The usual work-up of the orange mixture gave 1.70 g of crude oil. Gas chromatographic analysis (conditions as above) showed the presence of both m- and p-methoxyacetophenone.

Product Yield:	20.7%
% Meta-:	23.6 ± 3.0
% Para-:	76.4 ± 3.0

The Reaction of m--Anisylcadmium Iodide with Acetyl Chloride. To the Grignard reagent prepared from 0.24 g (0.010 mol) of magnesium (Baker) and 1.87 g (0.010 mol) of m-bromoanisole in a total of 50 mL of dry ether, which was refluxed for 30 min and stirred at room temperature for 60 min, was added 3.66 g (0.010 mol) of cadmium chloride. The organocadmium reagent was stirred for 90 min and 0.78 g (0.010 mol) of acetyl chloride in 30 mL of dry ether was added dropwise. The usual work-up gave 2.10 g of crude oil. Gas chromatographic analysis (conditions as above) showed the presence of both m- and p-methoxyacetophenone.

Product Yield:	31.8%
% Meta-:	21.8 ± 0.6
% Para-:	78.2 ± 0.6

The Reaction of Bromine with Anisole, with and without Cadmium Chloride and/or Magnesium Chloride. Four 100-mL round-bottomed flasks were assembled with magnetic stirrers and addition funnels and topped with

calcium chloride tubes. Each was charged with 1.08 g (0.010 mol) of anisole in 30 mL of dry ether. In Flask-1 was placed 0.94 g (0.010 mol) of magnesium chloride and 0.92 g (0.005 mol) of cadmium chloride. To Flask-2 was added 0.010 mol of magnesium chloride; to Flask-3 0.005 mol of cadmium chloride, and Flask-4 contained none of these salts. To each flask 1.60 g (0.010 mol) of bromine was added dropwise with rapid stirring. The bromine color started to disappear in the flasks containing cadmium chloride after 60 min. Disappearance of the bromine color in the remaining flasks began after 12 hr of stirring. Another charge of 1.60 g of bromine was added to each flask, and stirring was continued for another 20 hr. To each flask was added 25 mL of saturated sodium bisulfite and the contents stirred until the bromine color disappeared. The contents of each flask were separated and the ether layers were each, separately, washed with water, dried over $MgSO_4$ and rotary evaporated. Gas chromatographic analysis of each sample showed appreciable amounts of p-bromoanisole, identified by peak enhancement.

Reaction of m-Dianisylcadmium with Bromine. To the Grignard reagent prepared from 0.24 g (0.10 mol) of magnesium (Baker) and 1.87 g (0.010 mol) of m-bromoanisole in a total of 50 mL of dry ether, which was stirred under reflux until the magnesium had disappeared, was added 0.92 g (0.005 mol) of cadmium chloride. The organocadmium reagent was stirred for 30 min at reflux. Approximately 3 mL of the mixture was withdrawn from the reaction flask and worked-up in the usual manner. This was to be analyzed for the presence of unchanged bromoanisole (see below). To the cooled (ice water) solution rapid addition of 1.60 g (0.010 mol) of bromine caused evolution of heat. The mixture was stirred for 5 sec and then decomposed by rapid

addition of 25 mL of saturated $NaSO_3$ solution. The usual work-up gave 1.75 g of crude oil. Gas chromatographic analysis showed the presence of both m- and p-bromoanisole.

GC Conditions:	Column Temp:	125^0
	Detector Temp:	185^0
	Gas Flow:	60 mL/min
	Sample Size	1 μL
Retention times:	Meta-:	16.0 min
	Para-:	18.5 min
Yield Data:	Product Yield:	67.4%
	% Meta-:	73.8 ± 1.0
	% Para-:	26.2 ± 1.0

These chromatographic data were determined in a manner similar to that for methoxyacetophenones, with benzonitrile as an internal standard. Thus a graph was used whereby the corrected ratios could be read directly from the plot and then adjusted as described earlier When the 3 mL sample, that was abstracted prior to brominolysis, was analyzed by gc, the only product formed was anisole within retention time, 20 min; i.e., the m-bromoanisole arose from reaction of the organocadmium reagent and not simply unchanged starting material.

When the reaction was run with initial predrying of the reaction mixture using ethylene bromide and one equivalent of magnesium the following results were obtained:

Product Yield:	64.2%
% Meta-:	76.0 ± 1.6
% Para-:	24.0 ± 1.6

To 1.08 g (0.01 mol) of anisole in 25 mL of dry ether was added 1.60 g (0.01 mol) of bromine in a flask, which was then shaken for 5 sec. The bromine color was dispelled by shaking with 100 mL of 5% Na_2SO_3. The ether layer was separated, dried ($MgSO_4$) and rotary

evaporated. Gas chromatograpjic analysis showed the absence of p-bromoanisole.

The Reaction of o-Dianisylcadmium with Acetyl Chloride. To the Grignard reagent prepared from 1.20 g (0.050 mol) of magnesium and 8.55 g (0.050 mol) of o-bromoanisole in a total of 100 mL of dry ether, which was refluxed for 60 min and stirred at room temperature for 30 min, was added 4.60 g (0.025 mol) of cadmium chloride. After a reflux period of 60 min, a Gilman test showed the presence of Grignard reagent. Stirring was then continued for 10 hr, when a Gilman test was negative, and 3.93 g (0.050 mol) of acetyl chloride in 50 mL of dry ether was added. The mixture was refluxed for 30 min and the usual work-up gave 5.40 g of a crude oil. Gas chromatographic analysis showed the presence of only ortho-methoxyacetophenone, identified by the infrared spectrum of a collected sample.

Retention Time:	15.5 min
Column Temp:	150°
Detector Temp:	198°
Gas Flow:	65 mL/min
UNH ir:	23238
Sadtler ir:	20308

When the reaction was run for the first time (without performing the Gilman test) 5.1 g of a crude solid was obtained. Recrystallization from an ethanol/water mixture afforded a white solid, mp 123.5-125°; lit[167] mp 125°. Nmr analysis (UNH nmr: 6993) showed the solid to be o,o'-dimethoxymethylbenzhydrol; nmr ($DCCl_3$) δ 1.95 (s, 3, CH_3), 3.40 (s, 6, CH_3O), 4.72 (s, 1, OH), 6.60-7.60 (m, 8, ArH).

UNH ir:	23229
UNH nmr	6993

The Reaction of m-Ditolylcadmium with Acetyl Chloride. To The Grignard reagent prepared from 0.60 g (0.025 mol) of magnesium (Dow) and 4.28 g (0.025 mol) of m-bromotoluene in a total of 50 mL of dry ether, which was refluxed for 2 hr, was added 2.2 g (0.013 mol) of cadmium chloride, and stirring was continued for 30 min. Then 1.96 g (0.025 mol) of acetyl chloride in 15 mL of dry ether was added dropwise. This mixture was refluxed for 30 min, and the usual work-up gave 2.5 g of crude oil. Gas chromatographic analysis showed the presence of only meta-methylacetophenone, identified by infrared, (UNH 23327; Sadtler 22460) and nmr (UNH 7330; Sadtler 2758). Nmr ($DCCl_3$): δ 2.36 (s, 3, CH_3Ar), 2.53 (s, 3, CH_3CO), 7.10-7.72 (m, 4, ArH). The 2,4 dinitrophenylhydrazone derivative melted at 201°; lit[168] mp 207°.

Retention Time:	4.5 min
Column Temp:	151°
Detector Temp:	200°
Gas Flow:	80 mL/min

A second peak with retention time of 20.5 min, collected from the GC, remains unidentified at this time (UNH ir: 23326; UNH nmr: 7332); but it is not para-methylacetophenone; (Sadtler ir: 872). The normalized yield of ketone was 51.5%.

The Reaction of di-m-Fluorophenylcadmium with Acetyl Chloride. To the Grignard reagent prepared from 0.48 g (0.020 mol) of magnesium (Dow) and 3.50 g (0.020 mol) of m-bromofluorobenzene in a total of 50 mL of dry ether, which was refluxed for 60 min (all magnesium consumed), was added 1.83 g (0.010 mol) of cadmium chloride. After the mixture had been stirred at room temperature for 30 min, 1.57 g (0.020 mol) of acetyl chloride in 25 mL of dry ether was added dropwise, and stirring was continued for an additional 30 min. The usual work-up gave 2.5 g of

crude oil. Gas chromatographic analysis showed only the presence of m-fluoroacetophenone. The normalized yield was 82%.

GC Conditions: Column Temp: 168°
Detector Temp: 197°
Gas Flow: 90 mL/min
Retention Time: 2.4 min

UNH ir: 23254
UNH nmr: 7240
Sadtler ir: 21865
Sadtler nmr: N/A

nmr ($DCCl_3$) δ 2.50 (s, 3, CH_3CO), 6.88-7.60 (m, 4, ArH); 2,4-DNP (EtOH/H_2O) mp 220°; lit[169] mp 210°.

The Reaction of di-m-trifluoromethylphenylcadmium with Acetyl Chloride. To the Grignard reagent prepared from 0.25 g (0.010 mol) of magnesium (Dow) and 2.25 g (0.010 mol) of m-trifluoromethylbromobenzene in a total of 50 mL of dry ether, which was refluxed for 60 min, was added 0.93 g (0.005 mol) of cadmium chloride, and stirring was continued at room temperature for 30 min. Then 0.79 g (0.010 mol) of acetyl chloride in 25 mL of dry ether was added dropwise. The mixture was stirred for 90 min and the usual work-up gave 3.2 g of crude oil. Gas chromatographic analysis showed the presence of only m-trifluoroacetophenone, identified by ir and nmr.

GC Conditions: Column Temp: 168°
Detector Temp: 197°
Gas Flow: 90 mL/min

UNH ir: 23261
Sadtler ir: 21309
UNH nmr: 7241
Sadtler nmr: N/A
Normalized Yield: 84%

Nmr ($DCCl_3$) δ 2.59 (s, 3, $C\underline{H}_3CO$), 7.30-8.10 (m, 4, Ar$\underline{H}$). Semicarbazone (H_2O): mp 207-208°; lit[170] mp 205-206°.

The Reaction of di-m-Methylthiophenylcadmium with Acetyl Chloride. To the Grignard reagent prepared from 0.25 g (0.01 mol) of magnesium (Baker) and 2.03 g (0.01 mol) of m-bromothioanisole in a total of 50 mL of dry ether, which was refluxed for 18 hr, was added 0.92 g (0.005 mol) of cadmium chloride, and then refluxing was continued for 2.0 hr. Then0.78 g (0.01 mol) of acetyl chloride in 25 mL of dry ether was added dropwise. The mixture was stirred an additional 30 min and usual work-up gave 1.65 g of crude oil. Gas chromatographic analysis showed the presence of m- and p-methylthioacetophenone, identified by ir and nmr.

GC Conditions:	Column Temp:	168°	
	Detector Temp:	197°	
	Gas Flow:	90 mL/min	
	Retention Times:	Meta-:	9.0 min
		Para-:	12.4 min
Yield Data (normalized):	Product Yield:		29.8%
	% Meta-:		84.1
	% Para-:		15.9

	m	p
UNH ir:	25361	23363
Sadtler ir:	N/A	19439
UNH nmr:	7579	7587
Sadtler nmr:	N/A	23204

A semicarbazone was prepared from material collected from the next-to-the-last gc peak and recrystallized twice from an ethanol/water mixture, mp 183.5-184.0°.

Anal- Calcd for $C_{10}H_{13}N_3OS$: C, 53.81; H, 5.87; N, 18.82, Found: C, 54.07; H, 5.87; N, 18.66.

p-Deuterioanisole. A 3-necked, 250-mL round-bottomed flask containing 2.40 g (0.10 mol) of magnesium (Dow) was flame dried under nitrogen, and 18.7 g (0.10 mol) of p-bromoanisole in 100 mL of dry ether was added dropwise. After refluxing for 60 min and cooling, 5.0 g (0.250 mol) of deuterium oxide was added via a syringe and the mixture was stirred for 60 min. The solution was filtered, dried (Na_2SO_4) and concentrated in vacuo. Vacuum distillation afforded 9.0 g (83.5%) of p-deuterioanisole; bp 65-70° (0.5 mm); lit[171] bp 223° (756 mm). Nmr (neat) δ 3.60 (s, 3, CH_3O), 6.70-7.24 (AB quartet, 4.16, ArH J=8). Integration of the peaks showed 25% anisole-H and 75% p-D-anisole.

UNH nmr: 6366

DCl/D_2O Quenching of m-Dianisylcadmium-Acetyl Chloride Adduct. To the Grignard reagent, prepared from 0.24 g (0.010 mol) of magnesium (Baker) and 1.87 g (0.010 mol) of m-bromoanisole, in a total of 50 mL of dry ether, which had been refluxed for 60 min and stirred at room temperature for 30 min, was added 0.92 g (0.005 mol) of cadmium chloride. After refluxing for 30 min and stirring at room temperature for an additional 30 min, 2.0 g (0.020 mol, 2.0 mL) of 20% DCl in D_2O (Aldrich) was added via a dry-bag-filled syringe. After stirring for 90 min, the usual work-up afforded 2.1 g of crude oil. Gas chromatographic separation and nmr analysis showed that deuterium had also been incorporated into the aromatic rings of the ketonic product.

m-Methoxyacetophenone; nmr ($DCCl_3$) δ 2.50 (s, 0.6, CH_3CO), 3.76 (s, 3, CH_3O), 6.70-7.40 (m, 4, ArH), (UNH nmr: 7245, 7228).

p-Methoxyacetophenone; nmr ($DCCl_3$) δ 2.45 (s, 1.7, CH_3CO), 3.80 (s, 3, CH_3O), 6.72-7.88 (AB quartet, 3.4, ArH J=10), (UNH nmr: 7244).

Some starting material was recovered from the reaction mixture via gc separation and its nmr (UNH nmr: 7229) showed no evidence of ring deuteriation; nmr ($DCCl_3$) δ 3.58 (s, 3, (CH_3O), 6.45-6.91 (m, 4, ArH).

Deuterium Exchange in m- and p-Methoxyacetophenone. A. A solution of m-methoxyacetophenone (Aldrich) in $DCCl_3$ was placed in an nmr tube and 1 mL of 20% DCl in D_2O was added. The nmr spectrum was scanned at various times as the acyl proton peak height (δ 2.50) decreased. After 4 hr the ratio of methoxy protons to acyl protons was 3:2 (UNH nmr: 7204), and after 48 hr the ratio was 3:1 (UNH nmr: 7213). In a similar experiment with p-methoxyacetophenone, the peak ratio was 3:1.1 after 48 hr (UNH nmr: 7205, 7211).

B. A flame-dried 1-necked 100-mL round-bottomed flask containing 4.0 g of p-methoxyacetophenone, 4 mL of 20% DCl in D_2O and 50 mL of dry ether, was magnetically stirred for 2 hr. The usual work-up afforded 3.6 g of an oil. An nmr spectrum showed the ratio of the methoxy to acyl to aromatic protons to be 3.0:0.94:3.6; (UNH nmr: 7226).

Deuterium Exchange in m-Bromoanisole: Preparation of 2,4,6-Trideuterio-3-Bromoanisole. A flame-dried, 3-necked, 50-mL round-bottomed flask, fitted with a condenser topped with a $CaCl_2$ drying tube and a septum, was charged with 3.74 g (0.020 mol) of m-bromoanisole and 7 mL (0.25 mL) of 20% DCl in D_2O, introduced via a syringe, that was filled under nitrogen. After a reflux period of 19 hr, an aliquot was withdrawn via a syringe and placed into a test tube containing $DCCl_3$. A sample was pipetted from the $DCCl_3$ layer and passed through a pipet containing a glass wool plug and Na_2SO_4 and leading into an nmr tube. Inasmuch as the nmr spectrum of the effluent showed exchange, the remainder of the solution was extracted into ether, separated, washed with 5% $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo to give 3.70 g of an oil; nmr ($DCCl_3$) 3.60 (s, 3, CH_3O), 6.85 (s, 1.09, ArH), (UNH nmr: 7252).

The Reaction of 1-Methoxy-2,4,6-trideuterio-3-phenylcadmium Reagent with Acetyl Chloride. To the Grignard reagent, prepared from 0.24 g (0.10 mol) of magnesium (Baker) and 1.90 g of 2,4,6-trideuterio-3-bromoanisole in a total of 25 mL of dry ether, which had been refluxed for 60 min and stirred at room temperature for 30 min, was added 0.91 g (0.005 mol) of cadmium chloride. After stirring at room temperature for 90 min, 0.78 g (0.010 mol) of acetyl chloride in 25 mL of dry ether was added, and the mixture was stirred for 60 min. The usual work-up gave 1.5 g of a crude oil. Gas chromatographic separation yielded pure 3- and 4-methoxyacetophenones; 3- isomer: nmr ($DCCl_3$) δ 2.56 (s, 3, $C\underline{H}_3CO$), 3.81 (s, 3, $C\underline{H}_3O$), 7.26 (s, 1.19, Ar$\underline{H}$), (UNH nmr: 7329); 4- isomer: nmr ($DCCl_3$) δ 2.43 (s, 3, $C\underline{H}_3CO$), 3.77 (s, 3, $C\underline{H}_3O$), 7.77 (s, 1.0, Ar$\underline{H}$), (UNH nmr: 7310); the mass spectrum showed 46.1% d_2 and 39.2% d_3 for para; and 28.2% d_2 and 66.1% d_3 for meta; see Appendix.

The Attempted Preparation of m-N,N-dimethylaminophenylcadmium Reagent and Its Reaction with Acetyl Chloride. A. Normal Methods for Preparation of the Grignard Reagent: To a flame-dried, 3-necked, round-bottomed flask fitted with a condenser, mechanical stirrer and an addition funnel, and containing 0.60 g (0.025 mol) of magnesium (Baker) was added dropwise 5.0 g (0.025 mol) of m-bromo-N,N-dimethylaniline in 50 mL of dry ether. Gilman tests taken after 1 hr and 3 hr of refluxing were negative. When 1 mL of ethylene bromide was added, a reaction started immediately. After 1 hr of stirring the Gilman test was still negative. Next, there was added magnesium that had been activated by reaction with ethylene bromide in a test tube; again, after 1 hr the Gilman test was negative. Then 2 g of iodine crystals were added and after an hour $MgI_2 \cdot I_2$ was added. In each case the Gilman test was negative.

B. Sodium Naphthalide Method: This procedure is essentially that of Arnold and Kulenovic (172). To a 3-necked, round-bottomed flask, fitted with a mechanical stirrer, condenser and addition funnel, and containing 3.08 g (0.024 mol) of naphthalene in 20 mL of dry, peroxide-free THF, was added 0.46 g (0.02 mol) of sodium in small pieces under a nitrogen atmosphere. After stirring had been continued for 1 hr, 0.95 g (0.01 mol) of dry magnesium chloride was added in one portion. The dark green solution turned brown after 20 min, and 2.00 g (0.01 mol) of m-bromo-N,N-dimethylaniline in 20 mL of THF was added dropwise. A Gilman test was positive after 1 hr of refluxing. To the resulting red solution was added 0.92 g (0.005 mol) of cadmium chloride in one portion. After 30 sec the Gilman test was negative, and the solution turned gray. The THF was distilled and replaced by benzene. A solution of 0.79 g (0.01 mol) of acetyl chloride in 10 mL of benzene was added dropwise, there being no evidence of a vigorous reaction. After 2 hr, the mixture was hydrolyzed with 100 mL of 10% HCl and separated. The ether layer was washed with an additional 100 mL of 10% HCl, and the combined acid layers were washed with ether. The acid solution was neutralized (pH paper) with 15% NaOH and washed twice with ether. The ether was dried ($MgSO_4$) and rotary evaporated. Ir analysis of the crude oil showed the absence of ketonic products (UNH ir: 23402).

C. Active Magnesium Method: This procedure is essentially that of Reike (173). To a flame-dried, 3-necked, round-bottomed flask equipped with a condenser, mechanical stirrer and addition funnel, and containing 2.04 g (0.085 mol) of anydrous magnesium chloride (Alfa) in 50 mL of dry, peroxide-free THF, introduced via syringe, under a nitrogen atmosphere, was added 1.5 g (0.038 mol) of potassium metal in small pieces.

After the mixture had been held at reflux for 2 hr, 2.00 g (0.01 mol) of m-bromo-N,N-dimethylaniline was added dropwise. After 1 hr of reflux, THF was removed by distillation and replaced with benzene. A solution of 0.79 g (0.01 mol) of acetyl chloride in 15 mL of benzene was added slowly, and stirring was continued for another 30 min. Work-up with 10% HCl, followed by neutralization, filtration and extraction with ether, produced a crude oil whose ir spectrum showed the presence of two bands in the carbonyl region at 1695 cm^{-1} and 1740 cm^{-1} (UNH ir: 23273). A 2,4-DNP derivative was prepared and recrystallized twice from an ethanol/water mixture, mp 234-236°.

Anal. Calcd for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; H, 20.40. Found: C, 56.29; H, 4.26; N, 18.32. In repeated experiments with this method, a Gilman test never again was positive. Kugelrohr distillations of these reaction products gave only starting materials, hydrolyzed products, and ω-hydroxybutyl acetate, identified by ir comparison with the methyl ether published by Sadtler.

UNH ir: 23409
Sadtler ir: 15581

D. Lithium-Halogen Exchange: Into a 250-mL, 3-necked, round-bottomed flask, fitted with a condenser, mechanical stirrer and an addition funnel, was placed a solution of 200 g (0.01 mol) of m-bromo-N,N-dimethylaniline in 25 mL of dry ether. A 5-mL aliquot (0.01 mol) of a 2.4 M solution on n-butyllithium in hexane was placed in the addition funnel by way of a double-tipped needle and nitrogen pressure (174). The butyllithium was added to the solution at a rapid pace, and stirring and refluxing were maintained for 3 hr. An aliquot was withdrawn and hydrolyzed, and TLC showed almost complete lithium-halogen

exchange had occurred. To the yellow solution, which gave a positive Gilman test, was added 0.92 g (0.005 mol) of cadmium chloride. After a refluxing period of 1 hr, the Gilman test was still positive. Upon addition of 0.94 g (0.01 mol) of anhydrous magnesium chloride, the solution turned gray, but the Gilman test remained positive. Another 0.5 mol of cadmium chloride was added and after 1 hr of reflux the Gilman test was negative. After a solution of 0.78 g (0.01 mol) of acetyl chloride in 50 mL of dry ether had been added dropwise, stirring was continued for 30 min. Hydrolysis with water, followed by filtration, separation, drying ($MgSO_4$) and concentration in vacuo produced an oil whose ir (UNH ir: 23417) indicated the presence of some ketonic products. Preparative TLC on Silica Gel resulted in the development of three bands. Only the lower band (R_f=0.0-0.2) showed any ketonic products in the ir spectra. Kugelrohr distillation of the crude oil produced five fractions (A, low-boiling to 60°; B, 60-100°; C, 100-160°; D, 160-220°; and E, a brown, crystalline residue). Infrared analysis of the fractions showed that C, D, and E might contain some ketonic products (UNH ir: 23438, 23437, 23439). Nmr analysis of fractions B, C, D and E showed a doublet of methyl peaks at δ 2.78 and δ 2.85. The peaks may represent acetyl methyl protons and methyl amino protons (UNH nmr: 7732, 7744, 7745, 7746). The only reported derivatives for these ketones, m- and p-dimethylaminoacetophenones, are the oximes. Thus, attempts were made to obtain pure oximes from all five fractions. Only B and E gave solid oxime products. Recrystallization of these gave solids with wide melting points, 143-183° and 190-250°, respectively; lit[175] mp 79-80° for meta; lit[175] mp 220° for para.

The Reaction of m-Dianisylcadmium with Phenyl Cyanate. To the Grignard reagent prepared from 5.61 g (0.03 mol) of m-bromoanisole and 0.72 g (0.03 mol) of magnesium (Baker) in 50 mL of dry ether was added 2.75 g (0.015 mol) of anhydrous cadmium chloride. After a negative Gilman test was observed, 3.54 g (0.03 mol) of phenyl cyanate in 25 mL of dry benzene was added dropwise. The mixture was heated at reflux for 4 hr and then hydrolyzed with 10% HCl. A white precipitate was collected by suction filtration and recrystallized from a chloroform/hexane mixture, mp 230-231° (15%). Ir and nmr analyses showed the product to be phenyl cyanurate; lit[176] mp 224-225°.

UNH ir:	23418, 23433
Sadtler ir:	41797
UNH nmr:	7710
Sadlter nmr:	13819

The ether layer was separated and washed twice with 15% NaOH, dried ($MgSO_4$), and concentrated in vacuo. An infrared spectrum of the residue (UNH ir: 23416) showed the presence of nitrile (ν(C≡N) 2220 cm^{-1}). GC analysis showed one strong peak (I) at retention time 33.0 min and one smaller peak (II) with retention time 39.5 min, in addition to several peaks with low retention time. By collection of peaks I and II and spectrophotometric analyses it could be shown that II is p-methoxybenzonitrile (compared to the spectrum published by Sadtler). Peak I is tentatively assigned as m-methoxybenzonitrile. Its nmr spectrum shows the characteristics of a meta compound, and the ir spectrum shows a nitrile (ν(C≡N) 2222 cm^{-1}) and meta bands (ν(Ar-H) 750 cm^{-1} and 690 cm^{-1}). An attempt was made to oxidize the sample to the acid by sequential treatment with alkaline hydrogen peroxide and base, but this

was unsuccessful.

Gc Conditions:	Column Temp:	125°
	Detector Temp:	185°
	Gas Flow:	60 mL/min
Yield Data (normalized):	Product Yield:	38%
	% Meta-:	91%
	% Para-:	9%

	m	p
UNH ir:	23385	23385
Sadtler ir:	-	14300

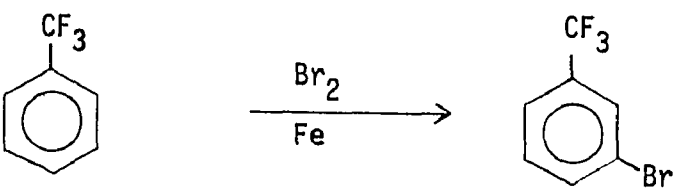
Investigation of the Reaction of m-Dianisylcadmium with Malonyl Dichloride. To the Grignard reagent prepared from 1.87 g (0.010 mol) of m-bromoanisole and 0.24 g (0.010 mol) of magnesium (Baker) in 25 mL of dry ether, was added 0.92 g (0.005 mol) of cadmium chloride. After a refluxing period of 30 min, when the Gilman test was negative, a solution of 1.41 g (0.010 mol) of malonyl dichloride in 25 mL of dry ether was added dropwise. Stirring was continued for 1 hr and then the mixture was hydrolyzed. The ether layer was separated, washed with 5% $NaHCO_3$, brine, and water, dried ($MgSO_4$) and concentrated in vacuo to give 48% residual oil. Its ir spectrum contained no bands in the carbonyl region. (The Sadtler spectrum for 1,3-indanedione shows bands at 1690-1750 cm^{-1} for the carbonyl stretches). The crude oil was heated with concentrated HCl for 1 hr. Again, after work-up, no ketonic products could be observed in the ir.

UNH ir:	23275, 23272
Sadtler ir:	3505 (for 1,3-indanedione)
Sadtler ir:	47448 (for 5-chloro-1,3-indanedione)

RESULTS AND DISCUSSION

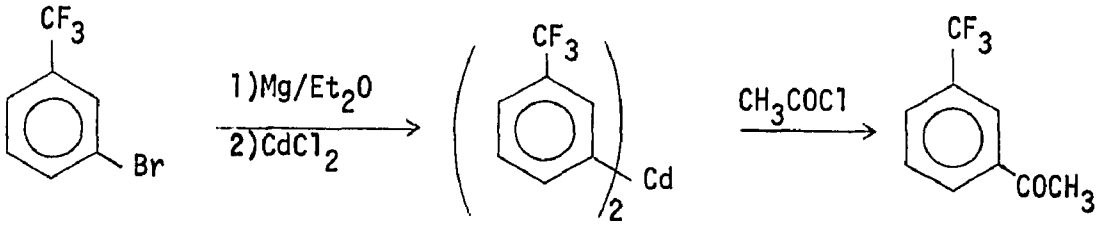
The purpose of this part of the investigation was to examine the scope and limitations of the organocadmium rearrangement first observed by Klemm and coworkers (1) and later elaborated by Dauben and Collette (2). It was decided to observe whether or not other substituents than the documented methoxy would lead to rearranged products and to what extent. Also we decided to test the methoxy compound and compare the results to those obtained by Dauben. Trapping agents other than acetyl chloride were chosen for reaction with dianisylcadmium. Changes in the composition of the anisylcadmium reagent were next considered for reaction with acetyl chloride to determine their effect on the rearrangement. Finally, experiments leading to the understanding of the rearrangement mechanism were performed.

Ring activating and deactivating groups were chosen so as to round out a survey of the aromatic substituents and determine their effect on the rearrangement. Inasmuch as the usual ring deactivating groups, such as nitro, carbethoxy, keto, could not be used, because of their incompatibility with the corresponding Grignard reagent, trifluoromethyl was chosen. The necessary reagent was prepared easily by bromination of α,α,α-trifluorotoluene in the presence of iron filings (159) (Scheme I). The Grignard formation proceeded smoothly with



Scheme I

spontaneous initiation, while only a small amount of magnesium remained unconsumed. After formation of the cadmium reagent, acetyl chloride was added dropwise with some refluxing (Scheme II).

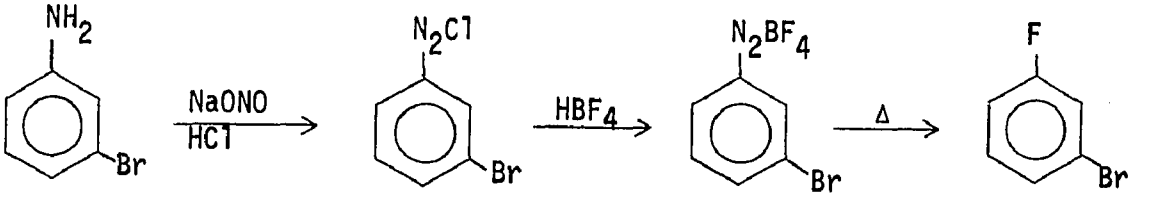


Scheme II

Gas chromatography of the isolated product showed one large peak at retention time 8.9 min and several smaller peaks with shorter retention times. Nmr and ir analysis of the last peak, isolated by multiple collections, showed it to be m-trifluoromethylacetophenone. The ir compared exactly to that published by Sadtler. The melting point of the semicarbazone corresponded to that cited in the literature (170). The gc elution was continued for an additional 20 min, but no further peaks were observed. The earlier peaks were shown to be ether, α,α,α-trifluorotoluene and unchanged m-bromo-α,α,α-trifluorotoluene.

Thus, strong ring deactivation leads to unrearranged product.

The fluoro group, which activates its para position slightly, was examined next. For this purpose m-bromofluorobenzene was required. Treatment of m-bromoaniline with nitrous acid gave the diazonium salt, to which was added fluoboric acid. The pink tetrafluoroborate salt was dried overnight and then decomposed with heat by means of a flame. Contrary to the literature description (157), the decomposition, once initiated, did not proceed spontaneously; instead repeated flaming was necessary to complete the conversion to the fluoro compound (Scheme III).



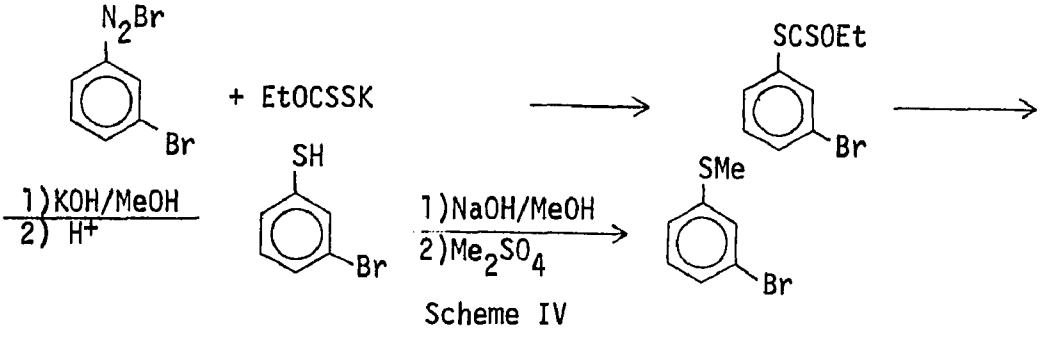
Scheme III

The Grignard reagent was formed efficiently, as indicated by disappearance of all the magnesium. Conversion to cadmium reagent and treatment with acetyl chloride followed as before. Gc analysis of the reaction mixture showed one large peak with retention time 2.4 min and several peaks which appeared earlier. These components were identified by peak enhancement to be ether, fluorobenzene and unchanged m-fluorobromobenzene, in order of emergence. No additional peaks were observed after continuation of the gc tracing for an additional 20 min. The peak with the longest retention time was collected. Its ir matched that published by Sadtler for m-fluoroacetophenone, and the 2,4-DNP derivative corresponded in melting point to that reported in the literature (169). In the nmr spectrum the aromatic multiplet was split into many sharp peaks due to the influence of ^{19}F coupling. No published spectrum was available for comparison. Although the fluoro group is known to activate its para position when on an aromatic ring, rearrangement was nevertheless not observed.

The mildly activating methyl group comparable to fluoro was then tested in this series of experiments. Reaction of acetyl chloride with the cadmium reagent, prepared from commercially available m-bromotoluene, produced an oil. Analysized by gc, this contained one large peak with retention time 4.5 min and several smaller peaks with earlier retention

time. Collection of the large peak from the gc and ir and nmr analysis showed it to be m-methylacetophenone. Both spectra matched those published by Sadtler. A 2,4-DNP derivative was prepared and its melting point compared well with that reported in the literature (168). The peaks with retention times less than 4 min were ether, toluene and unchanged m-bromotoluene. A small peak with retention time 20.5 min was collected and analysed by ir. Although its structure is not assigned, it can be shown not to be p-methylacetophenone by comparison with the Sadtler spectrum for that compound. This peak could represent p,p'-dimethylbiphenyl, or its meta isomers; but because it was produced in such small quantities, further analysis was not carried out. Thus the methyl group did not activate the organocadmium for rearrangement. Dauben, in his study, also found no rearrangement in the reaction of m-ditolylcadmium with acetyl chloride.

Methylthio was then considered for study because it is a strong ring-activating substituent. m-Bromophenylmethylsulfide was prepared by methylation of the sodium salt of m-bromothiophenol. This was obtained by basic hydrolysis of the corresponding xanthate, which in turn had been isolated from the reaction of ethyl potassium xanthate and m-bromobenzenediazonium chloride (Scheme IV). Ethyl potassium xanthate



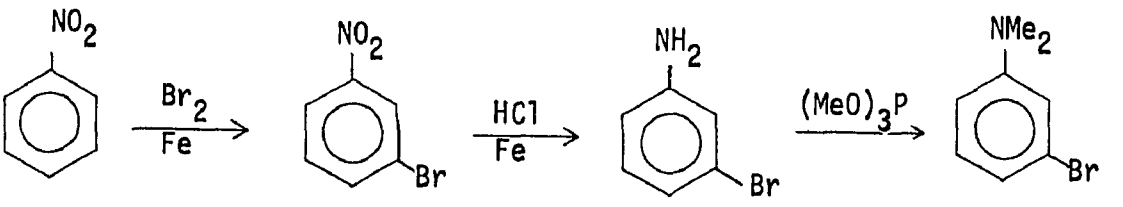
Scheme IV

is easily prepared by dissolving KOH in ethanol and adding carbon disulfide. In this reaction scheme the only products isolated were

m-bromothiophenol and its methyl thioether.

Reaction of the bromo compound with magnesium was not spontaneous. Instead, refluxing overnight in ether was necessary before a Gilman test was positive. When the corresponding cadmium reagent was prepared and allowed to react with acetyl chloride, a bright yellow solution was produced. Gc analysis of the crude, isolated product showed peaks that corresponded to ether, methylthionisole and unchanged starting material. Two other peaks with retention times 9.0 and 12.4 min were collected and analysed. The ir and nmr matched exactly the Sadtler spectra for p-methylthioacetophenone. The peak with retention time 9.0 min was assumed to be m-methylthioacetophenone, however no spectra for that compound could be found in the literature. A 2,4-DNP has been reported, but the melting point was 198^{0} which is the melting point of 2,4-dinitrophenylhydrazine. Consequently, instead of this derivative a semicarbazone was prepared whose elemental analysis was consistent with the structure. The extent of rearrangement was found to be 16% by gc analysis. Thus, ring activation by the methylthio group resulted in rearrangement, which, however, was less extensive than that promoted by methoxy.

The N,N-dimethylamino substituent, was considered as important group for study because of its strong ring activation. m-Bromo-N,N-dimethylaniline was synthesized stepwise from nitrobenzene as shown in Scheme V. Bromination of nitrobenzene and subsequent reduction in the presence of iron filings gave m-bromoaniline. Adaptation of an alkylation for the preparation of m-trifluoromethyl-N,N-dimethylaniline was employed (156) to give the aniline in good yield.



Scheme V

Preparation of the corresponding Grignard reagent by the usual means was unsuccessful, as indicated by a negative Gilman test. The mixture of m-bromo-N,N-dimethylaniline and magnesium turnings was subjected to prolonged refluxing and stirring; it was activated by iodine, then by $MgI_2 \cdot I_2$; entrainment was carried out with ethylene bromide, and with freshly reacting magnesium. In no case was there evidence for Grignard formation.

Attempts to prepare the Grignard reagent from active magnesium according to the method of Rieke (173) were likewise unsuccessful. According to his preparation, anhydrous magnesium chloride is reduced to finely divided magnesium metal by allowing it to react with potassium metal in THF at reflux. In only one case was a positive Gilman test noted after the bromo compound has been introduced.

Gc analysis and vacuum distillation of a portion of the isolated oil from this reaction mixture allowed the separation of starting material and the hydrolysis product, N,N-dimethylaniline. Also obtained was a compound, tentatively assigned ω-hydroxybutyl acetate, which could have resulted from THF ring opening. The assignment of this structure was based on its ir similarity to the Sadtler ir (15581) for ω-methoxybutyl acetate.

Another method for the reduction of magnesium chloride, sodium naphthalide being the reducing agent, was employed (172). A Gilman test was positive after the bromo compound had been added to the reduced magnesium in THF. After reaction of the corresponding cadmium reagent with acetyl chloride, work-up afforded an oil whose gc analysis showed only starting material and hydrolysed product. These results are not surprising in view of the report (177) that the Grignard reagent from p-bromo-N,N-dimethylaniline is extremely difficult to prepare. Even addition of 2.5 molar equivalents of iodine and 50 molar equivalents of ethyl bromide to an excess of magnesium turnings produced the Grignard reagent in only 60% yield. Other authors (178) have described p-bromo-N,N-dimethylaniline as a compound "inert to Grignard formation".

An alternative for formation of organometallics is halogen-metal interconversion. In fact, the reaction of n-butyllithium and m-bromo-N,N-dimethylaniline resulted in almost complete conversion to the lithium reagent after a reflux period of 4 hr, as shown by TLC of a hydrolyzed aliquot and a positive Gilman test. After the addition of cadmium chloride and a reflux period of 8 hr, the Gilman test remained strikingly positive. The test became negative only after the mixture had been treated with $MgCl_2$ and $CdCl_2$ and held at reflux for another 16 hr. Infrared analysis of the crude isolated product showed a band at 1715 cm^{-1}, indicative of a carbonyl. Preparative TLC showed four major bands. Those with R_f=0.0 to 0.2 again showed infrared stretching bands at 1715 cm^{-1}, (The carbonyl band for p-N,N-dimethylaminoacetophenone is at 1660 cm^{-1}, according to the Sadtler spectrum.) Although the ir may be indicative of the carbonyl for the meta isomer, no spectrum for that compound is available. Kugelrohr distillation of the remaining portion of crude

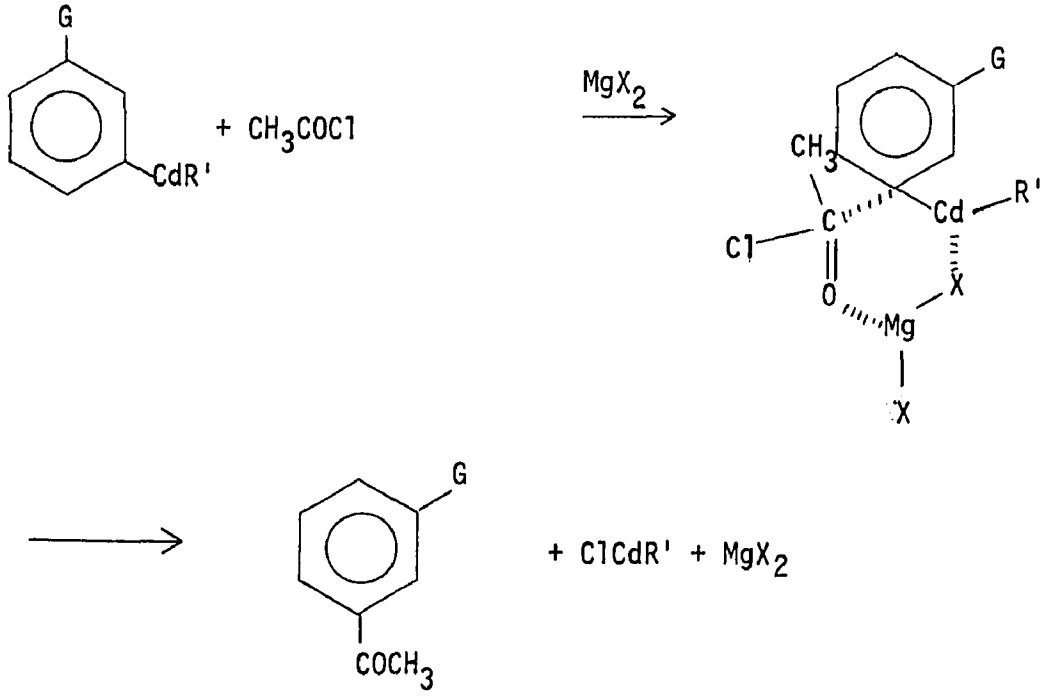
product provided five fractions. Infrared analyses showed that fractions A, C, D and E could have contained some ketonic products. Nmr analyses of these 5 fractions indicated that fractions B, C and D had two peaks in the methyl region at δ 2.78 and δ 2.84, (The Sadtler spectrum for p-N,N-dimethylaminoacetophenone shows singlets at δ 2.52 (CH_3CO) and δ 3.10 (NCH_3), and an AB quartet (ArH) centered at δ 6.72 and δ 7.95.) In none of the spectra were there any peaks at lower field than δ 7.50, and nothing could be identified as an AB quartet. Solid oximes could only be obtained from fractions C and E, their melting points being 143-183^0 and 190-150^0, respectively. The literature melting points for the oximes are 79^0 for the meta and 220^0 for the para. The broadness of the melting points for the oximes prepared here may be due to the presence of a mixture of E and Z isomers. Thus there is no evidence that a dimethylamino substituent promotes rearrangement. In fact, it is still uncertain as to whether or not a cadmium reagent was formed.

Reike's reduced magnesium method seems to hold the most promise, but it contains the serious drawback that THF is used as solvent, one which is subject to cleavage by organocadmium reagents. Perhaps magnesium chloride can be reduced in a different solvent such as diethylene glycol diether ether, which has the high boiling point needed to melt the potassium metal and yet is compatible with acetyl chloride organocadmium reactions.

The dianisylcadmium reagent was next prepared and allowed to react with acetyl chloride. The acetophenones were identified by peak enhancement on the gc and collection from the gc for ir and nmr analyses. These spectra matched those published for authentic samples. Because quantitative results were needed for the comparison, the gc was calibrated

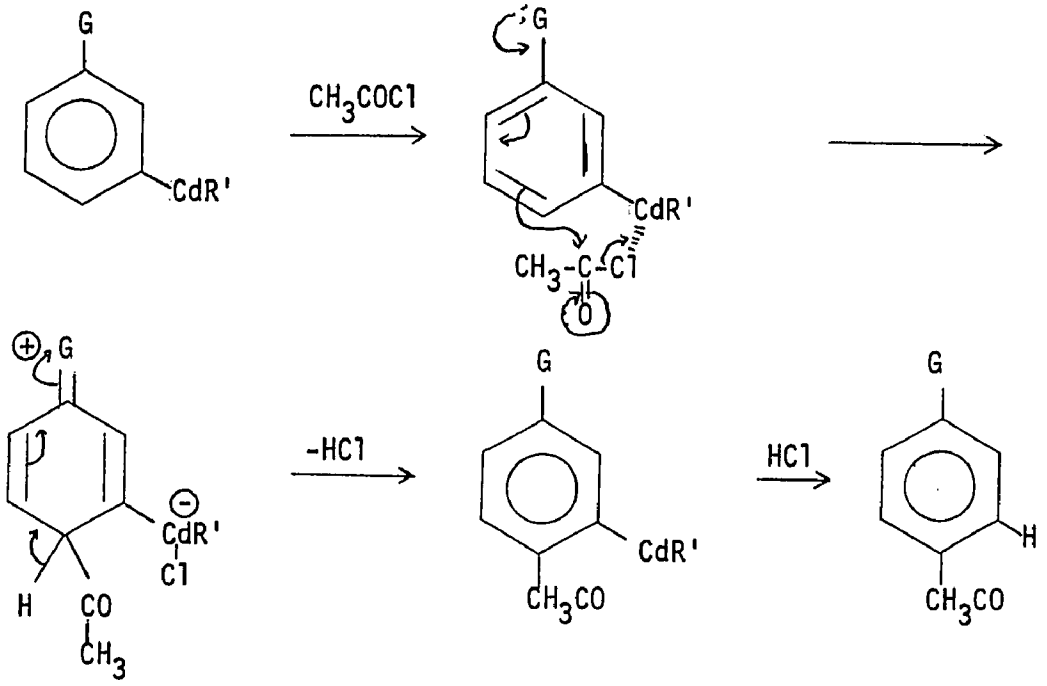
with known mixtures of m-methoxyacetophenone and biphenyl as the internal standard; and, similarly, p-methoxyacetophenone was calibrated against biphenyl. It should here be noted that the work by Dauben and Collette in 1950, using UV and 2,4-DNP derivatives techniques, correlates nicely with our work in 1978, using more sophisticated techniques: gc, ir, nmr; for Dauben and Collette obtained a 35%:65% ratio of m- to p-methoxyacetophenone, while, from our experiments a ratio of 26%:74%, meta:para was obtained.

The formation of "normal" and "abnormal" products can be visualized as proceeding by two different reaction pathways. On the one hand, the normal product results by way of the usual mechanism written for cadmium reagents (Scheme VI). The abnormal product results from participation of



Scheme VI

the ring substituent in an aromatic electrophilic substitution (Scheme VII). The question of the presence of an acetylated arylcadmium reagent will be addressed later.



Scheme VII

In an attempt to drive the reaction in favor of rearrangement, it was felt that magnesium salts could be removed from the solution, thus making them unavailable for aiding the "normal" reaction, as depicted in Scheme VI. The magnesium salts were precipitated as complexes of dioxane. Various attempts were then made to remove these complexes from the mixture, including suction filtration on a Büchner funnel under nitrogen and transfer of the solution to another round-bottomed flask by means of forcing the solution through a Guchi funnel fitted with a glass wool plug that was placed inside the reaction flask via suction. In both cases no filtration could be realized as the filters were plugged up quickly.

Thus acetyl chloride was added directly to the reaction flask containing the precipitated dioxane complex. It is not known if the dioxane complex is in equilibrium with the diethyl ether complex, thus making the salts soluble again, or if the salts become completely removed.

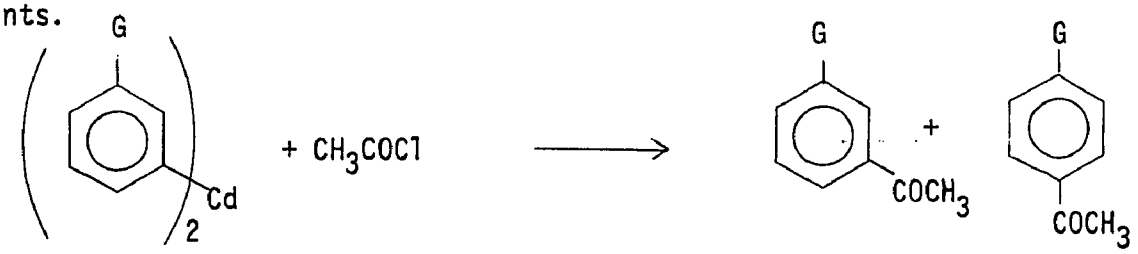
However, when the product was analysed, it was found that a decrease in rearranged product had taken place (62%:38%; para:meta). It would certainly be of interest to prepare "purified" dianisyl cadmium and allow it to react with acetyl chloride to see what the product ratio is.

It would seem that the groups that strongly activate their para positions would to some extent enhance formation of rearranged product. In a general way, then, the more the ring is activated by the substituent, the more driving force there is for rearrangement. It was of interest to look for a correlation between σ^+ values and rearrangement.

Table A lists the yields, ratios of products and ring activating constants for the reactions so far mentioned.

TABLE A

The Reactions of Acetyl Chloride with Variously Substituted Organocadmium Reagents.



G	σ^+	% Yield	Relative Ratio	
			Meta	Para
CF_3	0.52	84	100	0
F	-0.07	82	100	0
CH_3	-0.07	52	100	0
CH_3S	-0.24	30	84	16
CH_3O	-0.50	37,39	28,23	72,77
CH_3O*	-0.50	35	38	62
$(CH_3)_2N$	-1.70	X	X	X

* Precipitated magnesium salts prior to acetylation

X Inconclusive results.

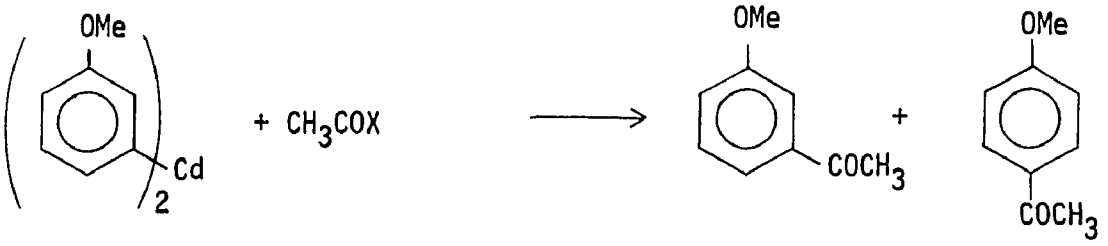
Indeed, of the substituents studied, the two with the most negative σ^+ values (179) are the ones leading to rearrangement. One would expect, then, the dimethylamino group to lead to the highest amount of rearranged product. Although it was not possible to analyze products from the m-dimethylamino reagent, the melting point behavior of the oxime derivatives suggests that the p-acetophenone may have been formed.

Next, we wanted to design other experiments to test the feasibility of Dauben's mechanism. It was felt that if the complexing of the leaving group of the acylating agent to the cadmium atom in the organocadmium reagent plays a major role in rearrangement, as in Scheme VII, then perhaps by changing the leaving group, the extent of rearrangement might be varied, and that this variation might be a function of the strength of the complex. Pearson's Hard and Soft Acid and Base Theory (180) (HSAB) can be invoked to explain the strength of complexes between electron donors and acceptors. Cadmium is known to be a soft acid, and, as a first approximation, acetylating agents RCOX, where X is soft, should form "strong" complexes and hence lead to more extensive rearrangement.

Acetyl chloride, acetyl bromide, acetic anhydride and diacetyl sulfide were chosen for comparison in this study. They represent acylating agents with a wide variety of leaving groups. According to Pearson's HSAB Theory bromide and chloride are borderline cases, neither soft nor hard. But oxides are hard, while sulfides are soft. Thus by this argument the most rearrangement should be noted with diacetyl sulfide, and the least with acetic anhydride.

TABLE B

The Reactions of m-Dianisylcadmium with Various Acylating Agents

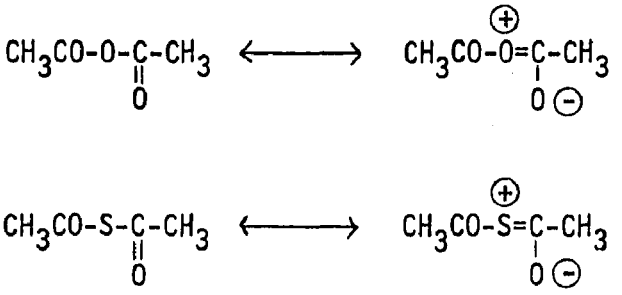


X	% Yield*	Relative Ratio	
		Meta	Para
$SCOCH_3$	18,31	100,100	0,0
Cl	37,38	28,23	72,77
Br	18,28	25,23	75,77
$OCOCH_3$	19,24	75,72	25,28

* Results are for duplicate experiments.

As can be seen from the results listed in Table B, HSAB Theory seems to hold for all but diacetyl sulfide. The borderline cases are similar in their amount of rearrangement, and acetic anhydride gives less rearrangement than the borderline cases. Perhaps other factors play the major role in the reaction of diacetyl sulfide. One possibility may be that the steric bulk of the sulfur to cadmium complex or the length of bonds, causes a shifting of the acetyl group out of position for attack at the position ortho to the cadmium atom.

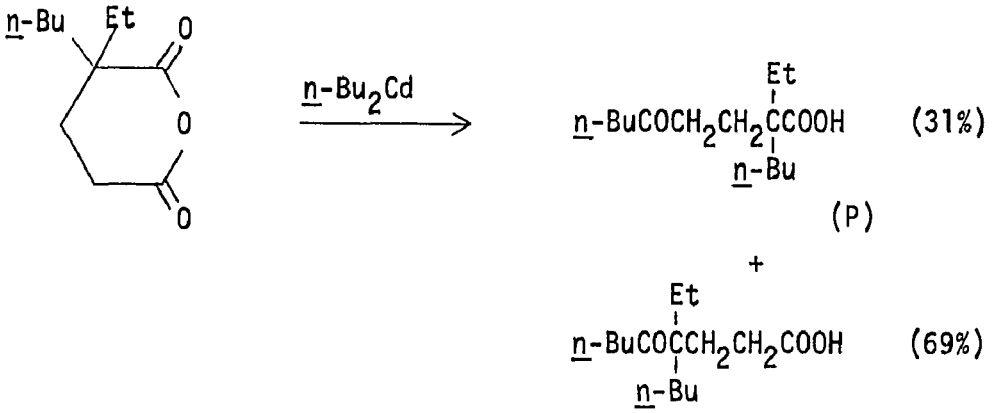
Electronic factors may be important as well. Thus an explanation for the smaller amounts of rearranged product observed with the anhydride maybe that the acetyl group exerts an electron-withdrawing effect on the α-substituent. It may be that dipolar resonance structures, as shown in Scheme VIII, may be large contributors to the electronic nature of these molecules. Thus the ability for these atoms to complex is weakened.



Scheme VIII

On the basis of current information it is difficult to assess the relative importance of these effects in diacetyl sulfide as compared to acetic anhydride.

The proposal that the cadmium atom complexes with the acetyl substituent and not the carbonyl has been supported by Cason (181). In the reaction of α-ethyl-α-n-butylglutaric anhydride with di-n-butylcadmium (Scheme IX), if one assumes that the cadmium atom complexes with the carbonyl oxygen, then formation of P would be expected to be the major product, since less steric hindrance would result from coordination with the carbonyl on that side of the molecule.



Scheme IX

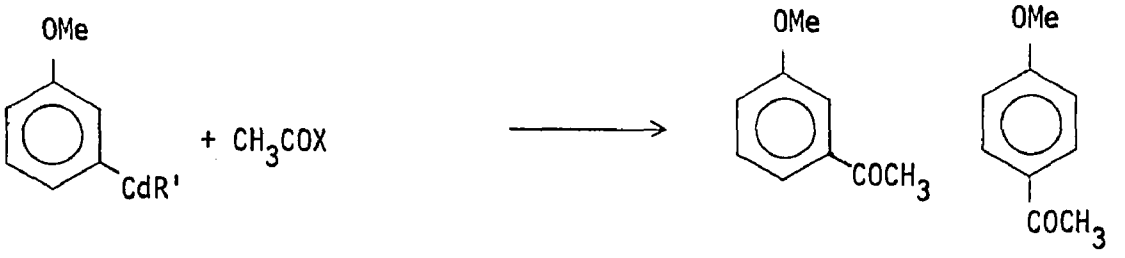
Thus it is postulated that cadmium initially coordinates with the central

oxygen, followed by breaking of the carbon-oxygen bond on the side favoring the less hindered cadmium carboxylate salt.

The next area to be investigated was that of varying the composition of the dianisylcadmium reagent and observe what effect this had on the rearrangement. Thus, organocadmium chloride, bromide and iodide (ArCdX,X=Cl,Br,I) were allowed to react with acetyl chloride and acetyl bromide, and the results are compared to those with the diorganocadmium (Table C).

TABLE C

The Reaction of Various Organocadmium Reagents with Acetyl Chloride and Acetyl Bromide.



R'	X	% Yield	Relative Ratios	
			Meta	Para
m-Dianisyl	Cl	37,31	28,23	72,77
m-Dianisyl	Br	29,18	25,23	75,77
Cl	Cl	41	25	75
Br	Cl	25	24	76
I	Cl	32	22	78
Br	Br	21	24	76

The results indicate that no significant change in the amount of rearrangement occurs when the type of organocadmium reagent is altered. It can thus be concluded that either the electronic structure about the cadmium atom is unaffected by these changes or, if electronic pertur-

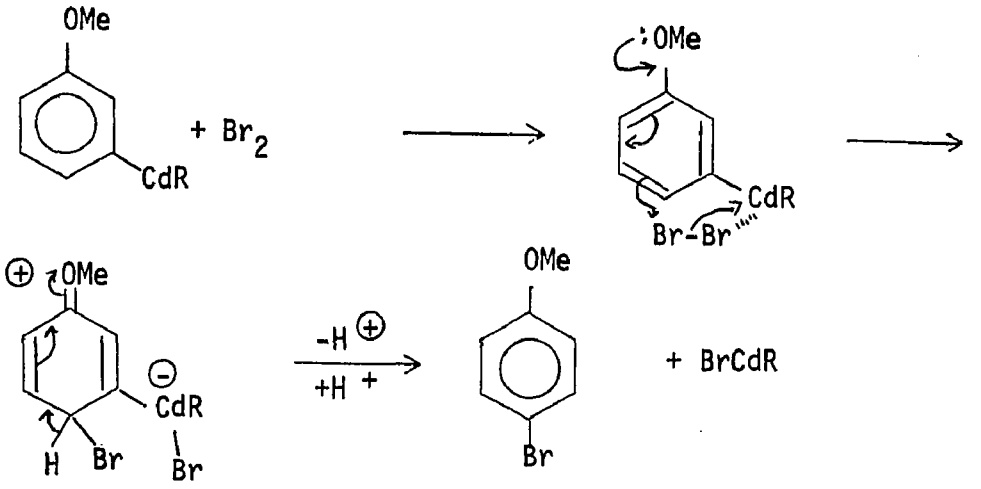
bation exists, these changes do not affect the amount of coordination between the cadmium atom and the acetylating agent.

Then we looked at trapping agents other than acetylating agents. A less familiar reaction of organocadmium reagents was performed in which m-dianisylcadmium was allowed to react with bromine to observe whether or not this trapping agent also gave rearranged product. For control experiments, two equivalents of bromine were added to anisole in ether containing equivalent amounts of magnesium and cadmium salts. After a 24-hr period, it was found that a substantial amount of p-bromoanisole was present, as determined by gc. Next, to determine whether the rate of this reaction was so fast that it would compete with brominolysis, anisole was treated similarly, but for a maximum time of 5 sec, the reaction being quenched with sodium bisulfite. Gc analysis showed that no p-bromoanisole had formed.

Thus bromine was added in one portion to a suspension of m-anisylcadmium and the mixture was immediately quenched with sodium bisulfite. To ensure that the amount of m-bromoanisole that might result was not merely that from unchanged starting material, an aliquot was removed from the Grignard mixture, which having been heated and stirred at reflux for 16 hr, contained no residual magnesium. Work-up and gc analysis showed that all the m-bromoanisole had been converted to the Grignard reagent.

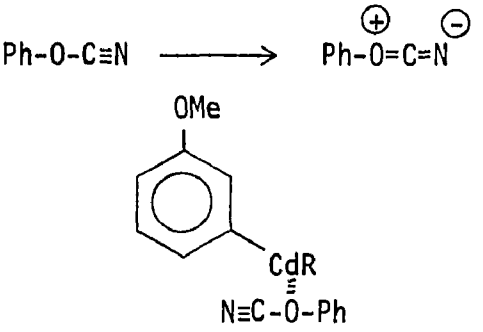
Gc analysis of the reaction product showed the presence of both m- and p-bromoanisoles, in a ratio of 25%:75%; meta:para.

Thus brominolysis leads to a substantial amount of rearrangement. By analogy with the acetylating agents, a mechanism can be proposed whereby one of the bromine atoms coordinates with the cadmium atom, followed by attack of the activated ring, as in Scheme X.



Scheme X

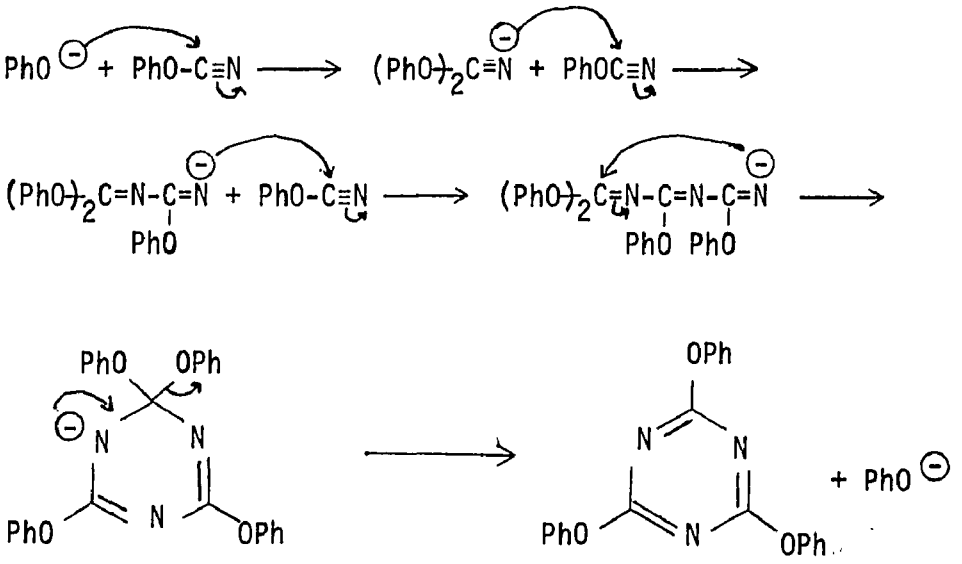
Another new reaction of cadmium reagents (more fully described later) is that with phenyl cyanate. This unusual reagent was allowed to react as a trapping agent for the rearrangement. It was found that 9% of the product nitrile was indeed p-methoxybenzonitrile. Here again the mechanism can be rationalized by an initial coordination of the cyanate oxygen to the cadmium atom, followed by attack by the activated ring. Several proposals can be made for the suppressed amount of rearranged product. HSAB Theory predicts that the oxygen is a hard base, and so coordination with the soft cadmium atom would result in a weakened bond. The electron-withdrawing influence of the nitrile on the oxygen may also make the electrons less available for coordination, inasmuch as a dipolar resonance contributor can be written (Scheme XI).



Scheme XI

Another factor that may be important is the linear geometry of phenyl cyanate; when coordinated with the cadmium atom, the nitrile group may be out of position for attack by the aromatic ring (Scheme X).

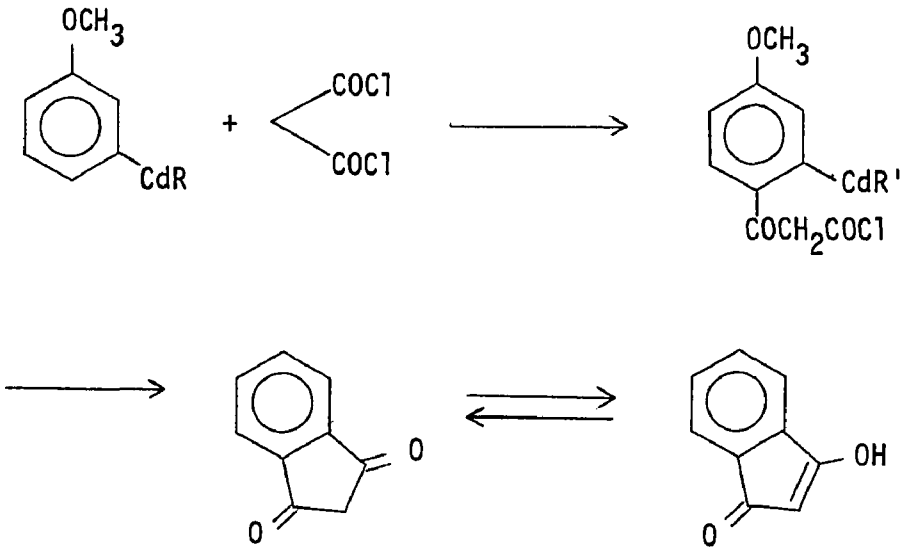
A side product of phenyl cyanurate was formed in 15% yield. This could have arisen in two ways. First, the phenyl cyanate may have trimerized on standing as it had been synthesized two months earlier and kept in a stoppered bottle, with no effort to keep it in the cold or in the dark. Second, in the reaction, phenoxide is formed as a by-product and may have catalyzed the trimerization during the reaction period (4 hr) as shown in Scheme XII.



Scheme XII

The cyanurate has the reported properties of insolubility in ether, water, acid and base. Its ir and nmr spectra and mp match those reported in the literature (see experimental, Part II B).

An attempt was made to utilize the difunctionality of m-dianisylcadmium, as Dauben had done, by its reaction with malonyl dichloride. As in the work of Dauben and Collette, an assumption is made that an intermediate results which still contains a carbon cadmium bond after the rearrangement step (Scheme XIII).

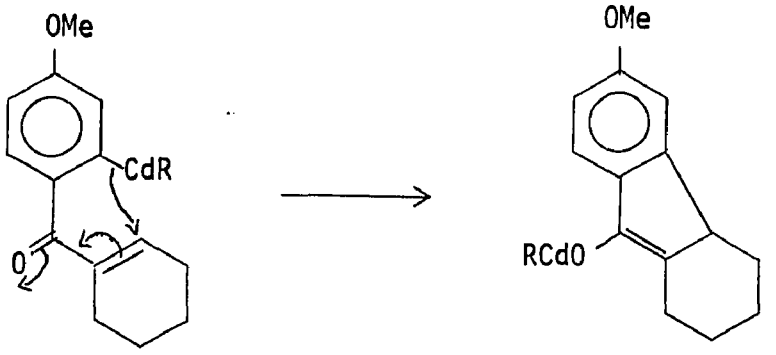


Scheme XIII

However when the reaction was run, no 1,3-indanedione was obtained; indeed no ketonic products could be observed by ir. The only materials isolated were unchanged starting material, anisole and malonic acid.

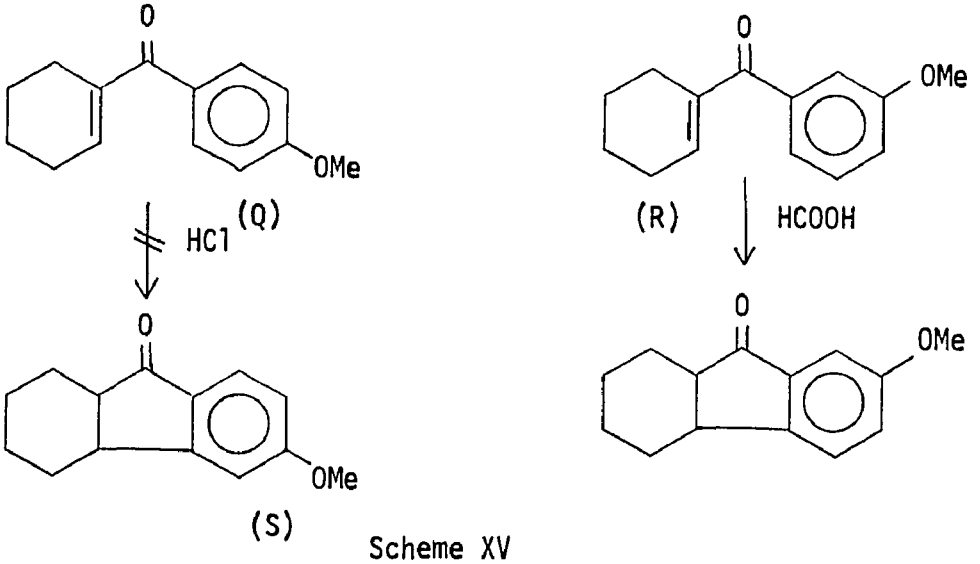
In the initial study by Dauben and Collette, cyclohexenyl-1-carbonyl chloride was allowed to react with m-dianisylcadmium. The product mixture contained, in addition to the 3- and 4-methoxytetrahydrobenzophenones (B and C, in Equation 1), a large amount of 2-methoxyhexahydrofluorenone (A, in Equation 1), which resulted from initial rearrangement of the acid chloride. To account for this product, Dauben and Collette proposed the formation of intermediate E

from the initial rearrangement to the benzophenone derivative. This then underwent 1,4 addition to the α,β-unsaturated ketone to give the fluorenone as in Scheme XIV.



Scheme XIV

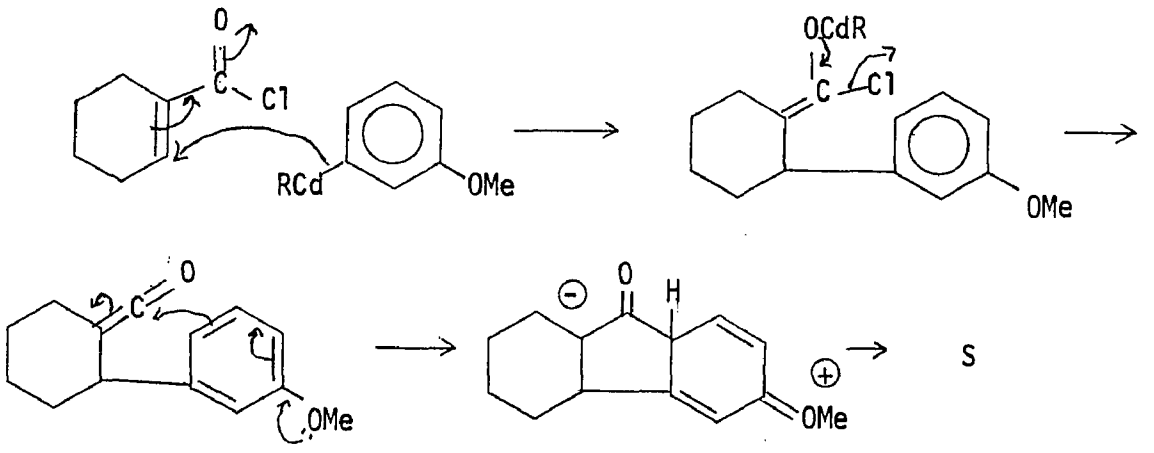
Formation of the final product, by a Friedel-Crafts-type reaction during work-up, was discounted since 4-methoxy-3',4',5',6'-tetrahydrobenzophenone (Q), when treated with acid, did not form any fluorenone while the 3- isomer (R) gave the corresponding fluorenone upon treatment with formic acid. These authors then compared the UV spectra of the authentic fluorenones with that obtained for the cadmium reaction mixture and found that the 3-methoxyfluorenone (S) was formed (Scheme XV).



Scheme XV

Furthermore the relative yields achieved in the reaction were reported to be 10% of the 3-methoxybenzophenone derivative (R), 50% of the 4- isomer (Q) and 40% of the 3-methoxyfluorenone (S).

These results then indicate that the rearrangement occurred to the extent of 90%. Other authors have claimed that the reaction of aromatic acid chlorides with m-dianisylcadmium gave 100% rearrangement. As a rationalization of these results, it seems possible that the cadmium reagent may have undergone a 1,4-addition to the double bond, this being followed by formation of a ketone and subsequent attack by the activated position of the aromatic ring (Scheme XVI).



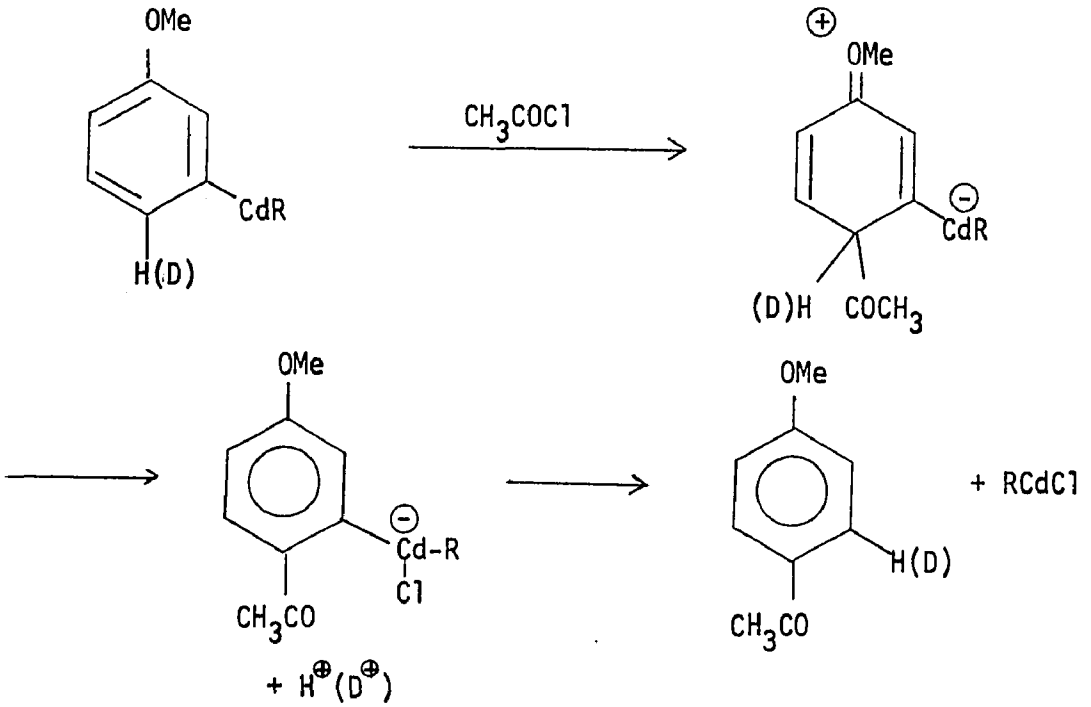
Scheme XVI

Although this type of transformation has not been observed for reactions of α,β-unsaturated acid chlorides, it cannot be discounted as a possible explanation for the results.

Because intermediate E was proposed as a possible intermediate in the reaction, an investigation was undertaken to determine whether that intermediate was feasible. Accordingly, 20% DCl in D_2O was used to

hydrolyze the mixture obtained from acid chloride treatment of m-dianisylcadmium. After work-up and gc separation, nmr spectra showed that no deuterium had been incorporated into the m- or p-methoxyacetophenones. If intermediate E was indeed present in the reaction mixture, deuterium should have shown up in the position of the carbon to cadmium bond.

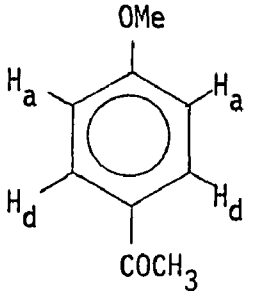
The possibility of the solvents providing the proton for hydrolysis was discounted when 3-methoxy-2,4,6-trideuterophenyl cadmium was allowed to react with acetyl chloride and hydrolyzed with 2N HCl. Gc isolation and nmr spectra showed 3-deuteriums in the aromatic ring and only one proton. The conclusion to be drawn from these results is that the acetyl chloride reacts to give the corresponding ketone with subsequent loss of HCl (DCl) as a by-product that hydrolyzes the cadmium-carbon bond (Scheme XVII).

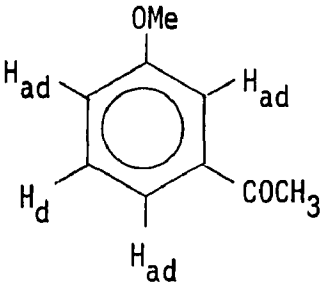


Scheme XVII

The mass spectra for these compounds seem to fit nicely with our earlier nmr results obtained from the DCl hydrolysis experiments. The integration of the aromatic protons is shown to be decreased, presumably due to ring exchange during work-up. The trideutero-4-methoxy compound was present in the amount of 39.3%, while the dideutero compound was 46.1% for the 4-methoxyacetophenone. This is not surprising since exchange could have taken place during the acid hydrolysis, some of the deuterium atoms in the 3 and 5 positions being replaced. These positions are activated by the methoxy group and, in comparison to the meta compound, are not deactivated by the acetyl group.

In the meta compound the trideutero compound was present in the amount of 67.6%, while the dideutero compound accounts for 27.2%. According to the proposed mechanism for "normal" cadmium reactions, the three deuteriums should have remained in position. Here again, however, some of the ring deuteriums were apparently exchanged during acid hydrolysis to give dideutero compounds. It is assumed that exchange in the meta product was less extensive than in the para product because the 2,4, and 6 protons in the former, although activated by the methoxy group, are deactivated by the acetyl group (see below).





a = activated
d = deactivated

During the course of this investigation, it was noticed that the nmr signal for the acetyl protons was substantially decreased. It was thought that some biphenyl was leaking through the gc and subsequently being analyzed in the nmr spectra. Some authentic p,p'-dimethoxybiphenyl was prepared and shown to exhibit an nmr spectrum distinct from that of the previous sample. Thus pure m- and p-methoxyacetophenones were placed in an nmr tube with 20% DCl in D_2O, and spectra were measured at various intervals. It was clearly shown that the acetyl protons exchange with deuterium over a period of 48 hr. In another experiment 20% DCl in D_2O was added to p-methoxyacetophenone in ether and allowed to react for 2 hrs under "normal" reaction conditions. Nmr analysis of the resultant product showed the spectrum to be identical to that obtained for the p-methoxyacetophenone from the reaction mixture.

To summarize, strong ring activating groups enhance the rearrangement of organocadmium reagents when reacted with acetyl chloride, while weakly activating and deactivating groups show no rearrangement. When different acetylating reagents were allowed to react with dianisylcadmium, differences in the amounts of rearrangement were observed. No change was noted when different types of anisylcadmium reagents were allowed to react with acetyl chloride or acetyl bromide. Dauben's proposed intermediate E seems inaccurate in light of the result that the proton (deuterium) in the position para to the activating group is lost prior to hydrolysis and finds itself available for hydrolysis of the carbon cadmium bond. Thus the route Dauben proposed for fluorenone formation is not completely accurate.

APPENDIX

Below are the mass spectral analyses (70 eV) for 2,3,5-trideutero-4-methoxyacetophenone (AA) and 2,4,6-trideutero-3-methoxyacetophenone (BB). These data were furnished by the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.

		m/e	% abundance	m/e	% abundance
AA	d_0	135	1.5	150	1.5
	d_1	136	10.7	151	11.2
	d_2	137	47.2	152	46.1
	d_3	138	39.1	153	39.3
	d_4	139	1.5	154	1.7
BB	d_0	135	0	150	0
	d_1	136	4.6	151	3.7
	d_2	137	29.2	152	27.2
	d_3	138	64.6	153	67.6
	d_4	139	1.5	154	1.5

PART II

NOVEL REACTIONS OF ORGANOCADMIUM REAGENTS

A. The Reactions of Indole Cadmium Reagents with Nonacidic Nitrosating Agents.

B. The Reactions of Aryl Cadmium Reagents with Aryl Cyanates.

C. The Reactions of Aryl Cadmium Reagents with Nitrosyl Chloride.

ABSTRACT

Indolylmagnesium iodide and indolylcadmium were allowed to react with nitrosyl chloride and isopentyl nitrite to give colorful mixtures of inseparable compounds. The 2-phenylindole derivatives gave 3-oximino-2-phenylindole. 2,3-Diphenylindolylcadmium, when allowed to react with nitrosyl chloride, gave yellow compounds, one of which gave a positive Liebermann test (N-nitroso).

It was shown that arylcadmium reagents react with aryl cyanates at ambient temperatures to give the corresponding nitriles in good to excellent yields.

When aromatic cadmium reagents were allowed to react with nitrosyl chloride, little or no nitroso compound could be obtained. Nitrosobenzene reacted with diphenylcadmium to give, among other things, diphenylamine and aniline.

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A

INTRODUCTION

Indole Grignard reagents have been known since 1910 (182), and their reactions with a multitude of substrates have been explored. The corresponding cadmium reagents, however, have not been reported in the literature. Thus work in our laboratories was undertaken to provide information in this area (183).

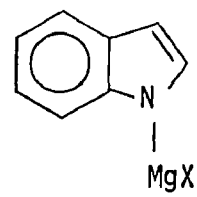
HISTORICAL

Although reactions of indole Grignard reagents are too numerous to mention here (184), attention can be drawn toward their reactions with acid chlorides and the structure of the Grignard reagent in solution.

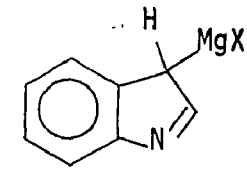
Indole Grignard reagents generally give 3-acetyl products when treated with acetyl chloride. In some cases significant amounts of 1,3-diacetyl compounds are formed. It has been reported that low temperatures favor the formation of the 1,3 products (185).

When the indole Grignard reagents are substituted in the 2-position by aryl or alkyl substituents, the products obtained are those substituted in the 3-position. Grignard reagents substituted in the 3- position react at 100^{0} to give the 2- substituted products and at ambient temperatures to give the N- substituted products, or a mixture of the two products, depending on the acid chloride. As expected, 2,3-disubstituted indole Grignards lead to the N- substituted products. Aralkyl acid chlorides give only the 3- substituted products, as do aryl acid chlorides with unsubstituted indole Grignard reagents (186).

The structure of indole Grignard reagents has received sporadic attention. Early investigation to determine whether the magnesium halide was bonded to nitrogen, as in T, or carbon, as in U, was based on the



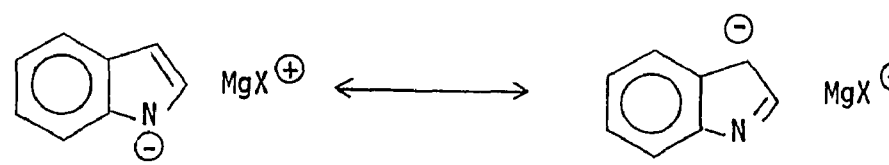
(T)



(U)

Gilman test. Nenitzescu (187), reporting that indolylmagnesium iodide gave a negative color test with Michler's ketone, considered this as evidence that structure T was the correct one. This conclusion was also based on the fact that the pyrrole Grignard reagent, which was considered to contain a carbon magnesium bond, gave a violet color with the test. However, Gilman cautioned that the Michler's ketone test can not be used to distinguish between C-MgX and N-MgX bonds (166).

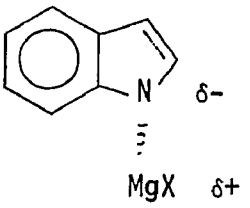
More recently, Katritzky and Lagowski (188) proposed an ionic structure with resonance hybridization (Equation 54).



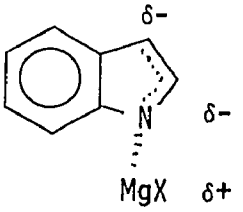
Equation 54

Reinecke and coworkers have performed nmr studies on the indole Grignard reagent and have proposed structures ranging from slightly

covalent V (189) to a resonance hybrid W (190).



(V)



(W)

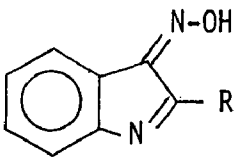
Solvent studies indicate that in ionizing solvents such as HMPT, the reaction of methyl halides with indolylmagnesium iodide occurs to a large extent on carbon, while in less ionizing solvents, such as toluene or THF, N- methylation is quantitative. Moreover, methylation occurs to a greater extent with methyl iodide than with methyl chloride in an HMPT/THF mixture (191).

Thus it seems that indole Grignard reagents contain an N-MgX bond which has a variable degree of ionic character affected by many external factors. ^{13}C and ^{15}N nmr studies should be of great value as a way to clarify this structural dilemma.

The problem of 1- versus 3- substitution has been studied more extensively with the alkali metal indoles. It has been shown that the 1- isomer becomes more abundant as the metal becomes more electropositive. Thus, the methylation of indolylpotassium occurs predominantly at the 1- position (87% relative yield) in toluene, while with the indolyllithium compound it is only 13% of the product (192). It is generally believed that, in alkylations at least, the more covalent species give C- alkylation (less hindered) and more ionic species give N- alkylation (most electronegative).

Other organometallic derivative of indoles include those of titanium, aluminum, calcium, zinc, mercury, silver, manganese and iron, although few if any of their reactions have been reported.

Of particular interest in the present investigation are the nitrosation reactions of indoles. Early workers reported that the reaction of indole and substituted indoles with various nitrosating agents gave the 3- substituted product. Campbell and Cooper (193) showed that the 3-nitrosoindole and its 2- substituted derivatives were in fact oximino compounds (Structure X).

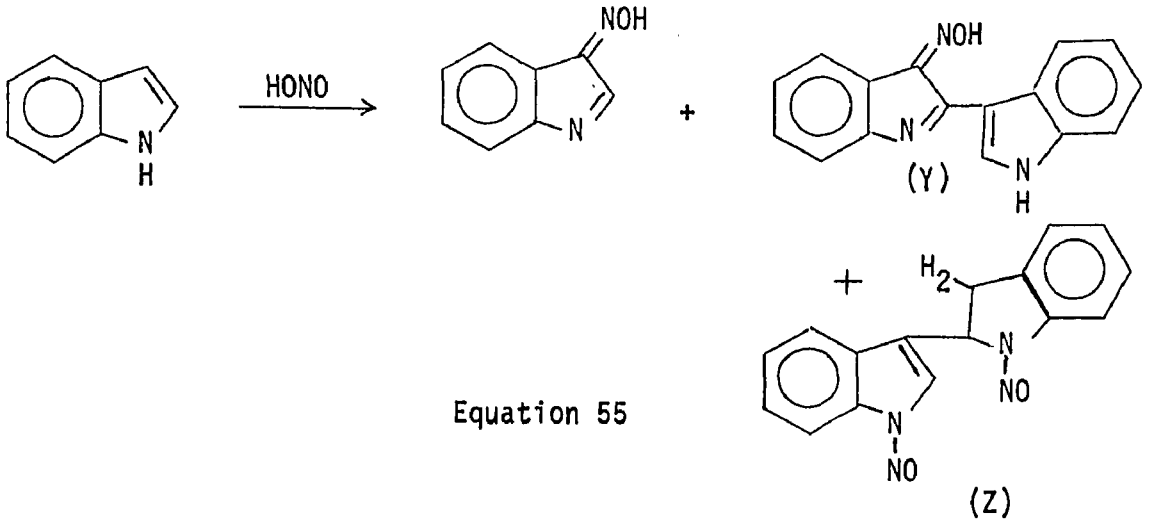


R = Alkyl, Aryl

X

If the indole is substituted on nitrogen, then these compounds are true nitroso compounds (see Table IX).

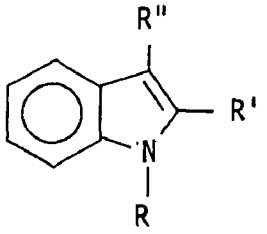
In the reaction of indole with nitrous acid (Table IX, entry #1). the main products, in addition to 3-oximinoindole, are indole red (Y) and the dinitroso-diindole (Z) (Equation 55). Oximinoindole has also



Equation 55

TABLE IX

The Nitrosation of Indole and Derivatives



Nitrosating Agent → Indole Products

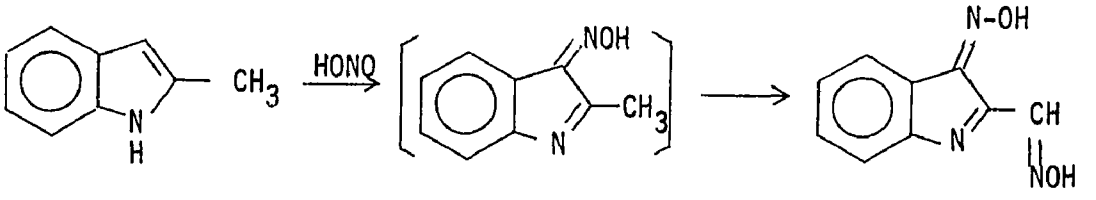
R	R'	R"	Nitrosating agent	Indole	References
H	H	H	HONO/AcOH	3-Oximino	194,195
H	H	H	NaOEt/n-PentylONO	3-Oximino	196
H	Me	H	HONO/AcOH	2-Methyl-3-oximino	197
H	Me	H	NaOEt/n-PentylONO	2-Methyl-3-oximino (87%)	198
H	H	Me	HONO	3-Methyl N-nitroso	194,199
H	Ph	H	HONO/AcOH	2-Phenyl-3-oximino	200
H	Ph	H	Alkyl nitrite	2-Phenyl-3-oximino	201
H	p-Tol	H	HONO/AcOH	2-p-Tolyl N-nitroso	202
H	p-PhPh	H	HONO/AcOH	2-p-PhPh-N-nitroso	202
Et	Ph	H	HONO/AcOH	3-Nitroso-2-phenyl-N-ethyl	203
Ph	Ph	H	HONO/AcOH	3-Nitroso-2-phenyl-N-phenyl	203
Me	Me	H	HONO/AcOH	2-Oximinomethyl-3-nitroso	203
H	Alkyl	Alkyl	HONO	N-Nitroso	194,202

been prepared from the condensation of 3-oxindole and hydroxylamine (193).

Although reactions of 2-arylindoles with nitrous acid were reported to give N-nitroso compounds (Table IX , entries 8 & 9), it is thought that the oximino compounds are in fact the actual products (204).

The reaction of 2-methylindole with nitrous acid (Table IX, entry 12) gives the 3-oximino-2-oximinomethyl indole as depicted in Equation 56. Initially, the probable product is the 3-oximino compound, which is then activated at the 2-methyl position toward further electrophilic substitution by the nitrosating agent.

There has been little recent work dealing with the studies of nitrosations of indoles, and there are no reported examples of organo-

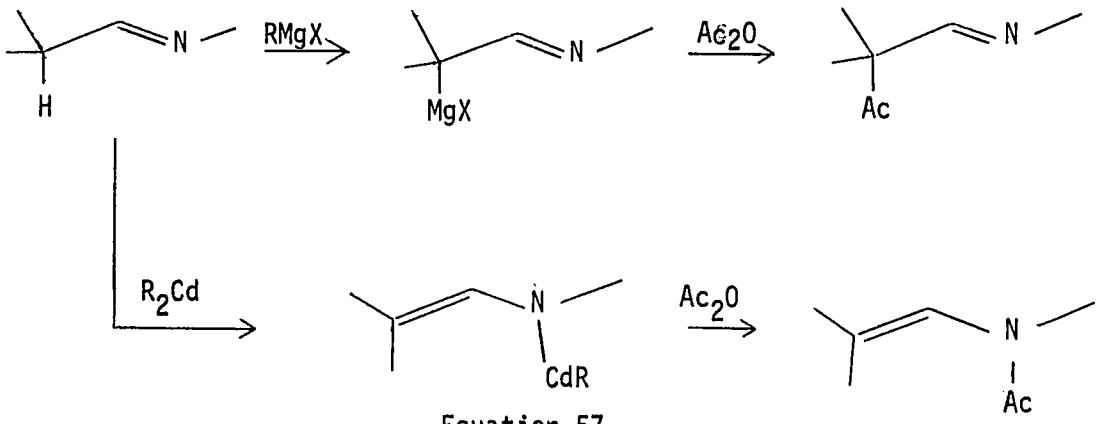


Equation 56

metallic indole reactions with nitrosating agents. This then is the subject of Part II A of this thesis.

It was thought that by analogy with acetyl chloride, nitrosyl chloride might give 3-substituted or 1,3- disubstituted products with indole organometallics. It has also been reported that treatment of Schiff bases with organocadmium reagents resulted in an acid-base reaction, with formation of a carbon-cadmium bond which when treated

with acetic anhydride, gave the N-acetylated product (205). In contrast, the Grignard reagent reacted under similar conditions to give the C-ace tylated compound (Equation 57).



Equation 57

Because the analogy to indoles was apparent, it was reasoned that treatment of the indole cadmium reagents with nitrosyl chloride might lead to N-nitrosoindole, a compound that has never before been synthesized.

EXPERIMENTAL

Indole and magnesium were obtained from J. T. Baker, cadmium chloride from VWR, methyl iodide and 2-phenylindole from Aldrich Chemical Co.

The general procedure for preparing the cadmium reagents has already been described in Part I, page 67.

Nitrosyl Chloride. This procedure is essentially that of Morton and Wilcox (206). A solution of 103.5 g (1.5 mol) of sodium nitrite in 100 mL of water was added to a filter flask containing 600 mL of concentrated HCl by way of an addition funnel that is attached to a tube fitted into a one-holed rubber stopper. The tube extended well below the surface of the magnetically stirred acid. The side arm of the filter flask was connected, in tandem, to three drying tubes containing, in order, sodium nitrite, potassium chloride (wetted to 2.4% with water) and calcium chloride. The last drying tube was connected to a gas collecting bulb that was kept in a Dry Ice-acetone bath during the reaction. Back pressure in the system was alleviated by stopping the flow of sodium nitrite for two-minute periods. After all the red-orange nitrosyl chloride had been collected in the Dry Ice trap, it was melted and transferred to a round-bottomed flask and connected to a special reflux condenser jacketed with a Dry Ice-acetone mixture. The red liquid was allowed to reflux for 1 hr. The acetone was then removed from the jacket by way of a spigot connected to the bottom of the condenser, and the gas was distilled into another gas bulb surrounded by Dry Ice-acetone. The nitrosyl chloride was stored in the cold mixture in a good hood because the gas is

very corrosive and toxic. The Dry Ice usually remained for 36 hr in a Dewar flask, at which time it was replenished. When needed, the solid was melted and poured into a graduated cylinder and used immediately. (Gloves should be worn at all times during manipulations with nitrosyl chloride). Yields ranged from 50-75%.

Isopentyl Nitrite. This procedure is an adaptation of that by Noyes (207). Into a 3-necked, round-bottomed flask, fitted with a mechanical stirrer, addition funnel extending to the bottom of the flask, and a thermometer, was placed 127 g (1.6 mol) of sodium nitrite and 500 mL of water. The solution was cooled to 0^{o} and a mixture of 35 mL of water, 45 mL of concentrated H_2SO_4, and 150 g (1.7 mol) of isopentyl alcohol, previously cooled to 0^{o}, was added dropwise, such that no gases were being evolved and the temperature was kept below $+2^{o}$. After the addition, two layers were allowed to separate and were filtered from residual solid into a separatory funnel. The top (organic) layer was separated, washed with $NaHCO_3$, brine and water, and dried (Na_2SO_4), to give 157 g (84%) of isopentyl nitrite. This was used without further purification.

2,3-Diphenylindole. This procedure is essentially that of Dolby and Rodia (208). A mixture of 32 g (0.15 mol) of benzoin, 48 g (0.51 mol) of aniline and 20 g (0.15 mol) anilinium hydrochloride was heated for 1 hr in a flask fitted with a reflux condenser. This mixture was cooled until semisolid; 150 mL of 2N HCl was added, and stirring was maintained for 3 hr. The solid that precipitated was collected by suction filtration, washed with 2N HCl, and recrystallized from ethanol to afford 29.6 g (69%) of pale yellow crystals; mp $123-124^{o}$; lit[208] mp $123-123.5^{o}$.

The Reaction of Indolylcadmium with Nitrosyl Chloride. A solution of 11.7 g (0.10 mol) of indole in 50 mL of dry ether was added to the Grignard

reagent prepared from 2.4 g (0.10 mol) of magnesium and 14.2 g (0.10 mol) of methyl iodide in 50 mL of dry ether. After the evolution of gas (CH_4) had ceased, 9.27 g (0.05 mol) of cadmium chloride was added in one portion as the solution turned to a gray-white suspension (Note: a Gilman test was not performed because it gives inconclusive results). A solution of 6.6 g (0.10 mol, 4.7 mL) of nitrosyl chloride in 50 mL of dry ether was added dropwise, whereupon a red precipitate was formed immediately. After the addition stirring was continued for 90 min and the mixture was poured onto 250 mL of 10% NH_4Cl. The precipitate was collected by suction filtration to give 16.7 g of a red powder.

This solid was subjected to a variety of separation techniques, all of which proved fruitless. A tlc separation on silica (9:1, $CHCl_3$: acetone) showed six spots. Column chromatography (Silica gel or Alumina), dry column chromatography (silica), preparative tlc (neutral alumina or silica) and HPLC did not result in any clean separations. Only crudely purified semisolids could be obtained. Sublimation and recrystallization from solvents including ethanol/water and pentane/ether mixtures likewise gave no clean separations, as was the case withSoxhlet extraction with hexane, chloroform or toluene. Reactions of indole cadmium chloride, indole in the presence of triethylamine, or indole alone with nitrosyl chloride gave very similar results.

The Reaction of Indole with Isopentyl Nitrite. To a magnetically stirred solution of 4.0 g (0.034 mol) of indole in 50 mL of 95% ethanol was added 4.0 g (0.034 mol) of isopentyl nitrite in one portion. The blood-red mixture was refluxed overnight with stirring. The red solid formed upon cooling was collected by suction filtration; 2.4 g; mp 157-158^{o} (dec). UNH ir: 23093; (ν(OH) 3400-2600 cm^{-1}; ν(C=N) 1300-1400 cm^{-1}, ν(ArH) 750 cm^{-1}).

The Reaction of 2-Phenylindolylcadmium with nitrosyl chloride. To the Grignard reagent prepared from 1.2 g (0.05 mol) of magnesium and 7.6 g (0.05 mol) of methyl iodide was added 8.6 g (0.05 mol) of 2-phenylindole in 25 mL of dry benzene. After the evolution of gas had ceased, 4.6 g (0.025 mol) of cadmium chloride was added in one portion. Stirring was continued for 30 min, when 3.3 g (0.05 mol) of nitrosyl chloride in 25 mL of dry benzene was added dropwise. When the addition was complete and stirring continued for an additional 30 min, a precipitate was collected by suction filtration. Tlc showed that the filtrate contained unchanged 2-phenylindole while the solid was a new product. Recrystallization from n-amyl acetate gave 8.7 g (80%) of gold crystals; mp 239-254° (dec); UNH ir 23093 (ν(OH) 2900-2000 cm^{-1}, ν(C=N) 1420 cm^{-1}, ν(N-O) 1060-960 cm^{-1}); lit[193] mp for 3-oximino-2-phenylindole, 280° (dec). Recrystallization from acetone gave gold crystals, mp 268-270° (dec).

3-Benzoyloximino-2-phenylindole. To a suspension of 100 mg of the gold crystals obtained above in NaOH was added benzoyl chloride. Extraction with ether, washing with water, drying (Na_2SO_4) and rotary evaporation gave orange crystals; mp 142-144°; lit[193] mp 153°.

3-Acetyloximino-2-phenylindole. A mixture of 200 mg of the gold crystals obtained above and 10 mL of acetic anhydride was heated on a steam bath for 30 min and cooled. Ether was added, the organic layer was separated, washed with $NaHCO_3$ and water, dried ($MgSO_4$) and rotary evaporated to give orange crystals; mp 111-114°; lit[193] mp 117°.

The Reaction of 2-Phenylindolylmagnesium Iodide with Nitrosyl Chloride. To the Grignard reagent prepared from 1.2 g (0.05 mol) of magnesium and 7.1 g (0.05 mol) of methyl iodide in 100 mL of dry ether was added 0.7 g (0.05 mol) of 2-phenylindole in 50 mL of dry ether. After this mixture

gas evolution had ceased, 3.85 g (0.021 mol) of cadmium chloride was added in one portion. After the mixture had been stirred for 1 hr and heated at reflux for 15 min, 2.75 g (0.042 mol) of nitrosyl chloride in 50 mL of dry ether was added dropwise. Stirring was continued for 1 hr, when 50 mL of water was added. The layers were separated; the organic phase was washed twice with water and once with brine, dried ($MgSO_4$) and concentrated in vacuo to a yellow oil. Tlc separation showed three spots. Column chromatography on silica gel of a portion of this mixture gave no clean separation of products, but the fraction containing the largest amount of yellow compound, that with R_f = 0.8, gave a positive Liebermann test for N-nitroso compounds (209).

The Reaction of 2,3-diphenylindole with Nitrosyl Chloride in the Presence of Triethylamine. To a magnetically stirred solution of 1.35 g (5 mmol) of 2,3-diphenylindole and 0.6 g (6 mmol) of triethylamine in 25 mL of dry ether was added 0.33 g (5 mmol) of nitrosyl chloride in 25 mL of dry ether. After being stirred for 30 min, the mixture was filtered and the solvent was evaporated to give 1.4 g of crude yellow solid. Tlc again showed three products in addition to unchanged starting material. Preparative tlc on silica gave three bands, the one with R_f = 0.85 giving a positive Liebermann test (209).

The Reaction of Indolylcadmium, Prepared from Dimethylcadmium, with Acetyl Chloride and Deuterium Oxide. To the Grignard reagent prepared from 0.72 g (0.03 mol) of magnesium and 4.26 g (0.03 mol) of methyl iodide in 25 mL of dry ether was added 2.3 g (0.015 mol) of cadmium chloride. After 30 min of stirring, 3.51 g (0.03 mol) of indole in 26 mL of dry ether was added dropwise as the solution turned bright yellow. Because no gas evolution was evident, the mixture was stirred and refluxed for 10 hr. After being cooled, approximately one-half of the mixture was transferred to another round-bottomed flask fitted with a

reflux condenser under a steam of nitrogen. To one flask was added 4.0 g (0.22 mol) of deuterium oxide, and stirring was continued for 18 hr. The ether layer was decanted, dried ($MgSO_4$), concentrated in vacuo and recrystallized from petroleum ether; mp 49-52°; lit[171] mp 52.5°. The crystals were calculated to be about 80% 1,3-dideuteroindole, based on nmr integration (UNH nmr: 7693). To the other portion was added 2.8 g (0.015 mol) of acetyl chloride in 10 mL of dry ether. Immediately a red precipitate formed, and after 30 min, it was collected by suction filtration. Recrystallization from water gave orange needles; mp 185-188°; (UNH ir: 23419; UNH nmr: 7692). The compound is tentatively assigned the structure of 3-acetylindole on the basis of the reaction of indole with acetyl chloride. In that experiment some indole in ether was added to a solution of acetyl chloride in ether. After about 1 hr the solution was red and a red compound had formed. Recrystallization of the filtered precipitate from water gave orange crystals; mp 184-188°; mmp 179-185°.

RESULTS AND DISCUSSION

The experiments described are the first examples of reactions of indoles with nitrosyl chloride and also the first examples of Grignard reactions with nitrosating agents. In addition, these are the first reports of cadmium derivatives of indoles.

It had been reported that with Schiff bases the organocadmium reagent produced an enamine which was metalated on nitrogen, as shown by the acetylation on nitrogen with acetic anhydride. It was thought that by analogy the cadmium atom might be bonded to the nitrogen preferentially and give N-nitroso compounds with nitrosating agents.

The reactions of indole organometallics with nitrosyl chloride are very colorful but extremely complex. Elaborate attempts at separations afforded only crude mixtures whose spectra were ambiguous. By analogy to past work, it is believed that the mixtures contain 3-oximino indole, indole, indole red, and the dinitroso-diindole, as is shown in Equation 55. Very little has been reported about these compounds so consequently information for comparisons is virtually nonexistent. As a matter of interest, the last reports of these compounds were in 1914 (196). More experimentation will be required before they can be properly characterized.

In the reaction of isopentyl nitrite with indole, there was formed a sharp melting, red solid, whose ir spectrum had the characteristics of an oxime. Recrystallization from ethanol and water gave a solid with melting point 125-157^{o}. Thus an analytical sample for elemental analysis was unavailable.

In all the other reactions involving indole and nitrosyl chloride, similar red compounds were formed whose TLCs were very similar.

It was then thought that 2-phenylindole would be a good model for these reactions. Indeed, the reactions of organometallic derivatives with nitrosyl chloride gave 3-oximino-2-phenylindole in good to excellent yields. Thus the prediction that the indole cadmium reagent would give mainly N-nitroso compounds from preferential bonding to the nitrogen was not borne out.

The use of reported (193) recrystallization solvent for the oximinophenyl indole derivative, n-amyl acetate (bp 180°), afforded orange crystals with a broad melting point. It was found that acetone was a superior solvent for these recrystallizations, glossy gold crystals with sharp melting points being obtained.

It is possible that some N-nitroso-2-phenylindole was formed in these reactions. Indeed, TLC of the filtrates showed there to be three other compounds present. Again, chromatographic separations were unsuccessful.

In the reaction of 2-phenylindolylmagnesium iodide with nitrosyl chloride, a gray-green solid was isolated from the filtrate in small quantity. This may be a C-nitroso compound from reaction with the aromatic ring, since C-nitroso compounds are characterized as being blue-green solids. Ir analysis did not give any conclusive results.

It is unknown why the reaction of nitrosyl chloride with 2-phenylindole gave a quantitative yield of yellow crystals with a low melting point. The ir spectrum is characteristic of the 3-oximino compound. Perhaps some impurities were present that caused a lowering but not broadening of the melting point.

Although no pure compounds were obtained from the reaction of 2,3-diphenylindolylcadmium with nitrosyl chloride, a positive

Liebermanns test was observed with the fastest moving fraction on TLC. In this test a sample is added to a solution of phenol in concentrated H_2SO_4. A dark blue color indicates the presence of an N-nitroso compound. This test is negative for C-nitroso compounds, oximes and nitro compounds. Indeed, a negative test was observed when 3-oximino-2-phenylindole was tested. Thus it is suspected that some N-nitroso compound in an impure state was obtained.

The reactions of indole compounds with methylmagnesium iodide are accompanied by evolution of a gas, presumably methane. Subsequent addition of cadmium chloride presumably gives the cadmium reagent. When dimethylcadmium was allowed to react with indole derivatives, no evolution of gas was observed, even over long periods of time. Although dimethylcadmium is reported to be very reactive, this result suggests that it is not as strong a base as the Grignard reagent. This finding is in direct contrast to the Schiff base reactions, which depend upon the acid-base nature of the reactants.

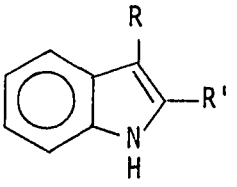
Because the Gilman test is inconclusive for these organometallics (i.e. indole Grignard reagent does not give a positive reaction), formation of the cadmium reagent can not be unambiguously verified. It is thought that the cadmium atom exchanges with magnesium in the indole series because a gray suspension is formed when cadmium chloride is added to the Grignard solution. However, no gray precipitate was formed when dimethylcadmium was allowed to react with indoles.

The deuteriation and acetyl chloride reactions are inconclusive inasmuch as indoles are known to react with D_2O without any external influences and it was shown that acetyl chloride reacts with indole in a manner similar to that of the indole cadmium reagent.

Table X lists the reactions and yields of the various indole compounds with nitrosyl chloride.

TABLE X

The Reactions of Indoles with Nitrosyl Chloride



Conditions → Indole Products

R	R'	Conditions	% Yield[a]	Indole Product
H	H	Cadmium	XX	XX
H	H	Cadmium chloride	XX	XX
H	H	Triethylamine	XX	XX
H	H	Ether	XX	XX
H	H	K_2CO_3	XX	XX
H	Ph	Cadmium	80	3-Oximino
H	Ph	Grignard	34	3-Oximino
H	Ph	Triethylamine	30	3-Oximino
H	Ph	Ether	XX	XX
Ph	Ph	Cadmium	XX	N-nitroso
Ph	Ph	Triethylamine	XX	N-nitroso

(a) XX means inconclusive results.

It is interesting to note that of all the reactions of 2-phenylindole with nitrosyl chloride, the one with the cadmium derivative leads to products in highest yield. Perhaps this is further support for the formation of the indole cadmium species.

In summary, reactions of indole with nitrosyl chloride gave complex mixtures which could not be totally identified because of the difficulty of their separation. The 2-phenylindole derivatives gave 3-oximino-2-phenyl indoles and perhaps some N-nitroso compounds. 2,3-Diphenylindole reagents presumably give N-nitroso derivatives, although their structures were not unambigously identified. The problem of the formation and structure of the indole cadmium reagent may best be solved by spectroscopic studies, in particular, ^{13}C and ^{15}N nmr.

with formation of a variety of imidourethanes and N-heterocycles. Aryl cyanates are indeed versatile reagents.

It should be mentioned that alkyl cyanates are distinctive, for they generally react with nucleophiles in an S_{N2} manner with loss of cyanate ion (212).

The reactions of carbon nucleophiles are less numerous, as very few reactions having been reported in the literature. Two German groups simultaneously reported the reactions of carbon nucleophiles with aryl cyanates. Each allowed Grignard reagents, enamines, and sodio malonic ester derivatives to react with aryl cyanates. Martin and Rackow (213) claimed that two equivalents of Grignard reagent were required for formation of the nitrile because the second equivalent was necessary for Lewis acid complexation of the nitrogen. These authors, however, found that the second equivalent of Grignard was also detrimental to the reaction, as it reacted with some of the product nitrile to give symmetrical ketones. Grigat (214) reported that the reaction of phenylmagnesium bromide with phenyl cyanate (1:1 reactant ratio) at -50^{o} gave a nitrile in 61% yield. Martin and coworkers also reported the reaction of ethyl cyanate with aryl and alkyl Grignard reagents. Whereas arylmagnesium halides gave only nitriles, the alkyl derivatives gave hydrocarbons, presumably from S_{N2}-types displacements.

Holm and Huge-Jensen (215) performed an extensive study on the reactions of alkyl and aryl Grignard reagents with alkyl and aryl cyanates. The yields of the corresponding nitriles varied from 34% for tert-butylmagnesium chloride and isobutyl cyanate to 92% for tert-butylmagnesium chloride and phenyl cyanate. It should be mentioned that the Grignard reagent was added inversely to the solution of cyanate, held at -78^{o}. In none of these Grignard reactions could the imidate salt,

formed from the initial addition across the nitrile, be isolated.

Other carbon nucleophiles that have been allowed to react with cyanates include enamines (to give α-cyanoketones), pyrroles in acid media (to afford 2-cyanopyrroles), and the sodium salts of a variety of malonic acid derivative, ranging from malononitrile to diethyl malonate and ethyl acetoacetate. This last set of reactions give the 2-cyano compounds. Interestingly, the malononitrile formed cyanoform.

The advantages of aromatic nitrile formation from the reaction of Grignard reagents are manifold. It is a directed synthesis from readily available reagents. One of the alternative methods of aromatic nitrile formation is the Sandmeyer reaction, involving diazonium salts and cuprous cyanide. This route involves the inherent drawback that some aniline compounds are expensive, especially those with substituents on the ring, and the yields are usually moderate. Other methods include pyrolysis of arenesulfonates in the presence of sodium cyanide, nucleophilic aromatic substitution on deactivated rings, and the Rosenmund-von Braun reaction, whereby aryl bromides are allowed to react at high temperature with cuprous cyanide.

Although the formation of nitriles from aryl Grignard reagents and aryl cyanates holds some promise, the low temperatures and sophisticated procedures involved detract from its value as a general method. Thus a study was initiated to determine whether organocadmium reagents could be used to better advantage in the reaction with aryl cyanates. This is the subject of Part II-B of this thesis.

EXPERIMENTAL

All spectra were obtained from instruments already described in Part I and were compared to Sadtler spectra where appropriate. The reagents used were obtained from Aldrich Chemical Co. unless otherwise noted. All temperatures are recorded in degrees Centigrade. All purified products were analyzed by gc and found to be 90-99+% pure. Contaminants were starting material, identified by peak enhancement, and phenol, identified by gc collection and ir analysis (UNH ir: 23492; Sadtler ir: 843).

Gc Conditions:	Column Temp:	178°
	Detector Temp:	189°
	Gas Flow:	100 mL/min

All retention times are noted in the appropriate sections. All yields are based on the amount of cadmium reagent formed, i.e. the unchanged starting material was subtracted from the amount used intially and the yields were then calculated.

Phenyl Cyanate. This procedure is essentially that of Vowinkel and Baese (216) and is slightly different from that reported in Part I. To a solution of 15.9 g (0.06 mol) of cyanogen bromide in 200 mL of dry ether, held at -10° in a Dry Ice-acetone bath and with strong mechanical stirring, was added dropwise a solution of 14.7 g (0.15 mol) of phenol and 15.1 g (0.15 mol) of triethylamine in 200 mL of dry ether over a period of 30 min. The temperature was not allowed to exceed -10°. After the addition and 30 min of additional stirring, the mixture was filtered by suction, the filtrate dried ($MgSO_4$) and concentrated in vacuo. Kugelrohr distillation afforded 24.6 g (61%) of phenyl cyanate(UNH ir: 23478).

This was stored in the refrigerator and protected from light.

4,4'-Dihydroxybiphenyl-bis-cyanate. To a rapidly stirred solution of 2.12 g (0.02 mol) of cyanogen bromide in 50 mL of dry ether, kept at -5°, was added a solution of 2.02 g (0.02 mol) of triethylamine and 3.72 g (0.02 mol) of 4,4'-dihydroxybiphenyl. After the addition and 30 min of stirring, the precipitated triethylammonium bromide was removed by suction. The filtrate was washed with 15% NaOH, dried ($MgSO_4$), and the solvent was evaporated, to give 3.5 g (74%) of a white solid; mp 136-137°; lit[216] mp 133-135°.

p-Methoxybenzonitrile. To di-p-anisylcadmium (0.025 mol) formed in the usual manner was added 3.0 g (0.025 mol) of 4,4'-dihydroxybiphenyl-bis-cyanate in 25 mL of dry ether. Heat was generated and a white precipitate formed. After addition, the mixture was refluxed for 30 min, cooled, and poured into 100 mL of 10% HCl. Work-up and Kugelrohr distillation afforded 1.33 g (40%) of product; mp 56-58°; lit[171] mp 61-62°. Gc retention time was 7.5 min.

UNH ir: 23480
Sadtler ir: 14300

o-Tolunitrile. To 0.025 mol of di-o-tolylcadmium, prepared as previously described, was added 3.0 g (0.025 mol) of phenyl cyanate in 25 mL of dry ether. The reaction proceeded as above, and the mixture was hydrolyzed in the flask with 25 mL of 10% HCl. The usual work-up afforded 2.6 g of crude oil and 2.2 g (75%) after Kugelrohr distillation; gc retention time, 2.0 min.

UNH ir: 23484
Sadtler ir: 2898

m-Tolunitrile. To 0.025 mol of di-m-tolylcadmium, prepared as previously described, was added 3.0 g (0.025 mol) of phenyl cyanate in 25 mL of dry

ether. Hydrolysis in the flask with 30 mL of 10% HCl, followed by work-up and Kugelrohr distillation, gave 2.15 g (73%) of a colorless oil; gc retention time, 2.5 min.

UNH ir: 23487
Sadtler ir: 2886

p-Tolunitrile. To 0.025 mol of di-p-tolylcadmium prepared as above was added 3.0 g (0.025 mol) of phenyl cyanate in 25 mL of dry ether. Hydrolysis in the flask with 25 mL of 10% HCl, work-up in the usual manner and Kugelrohr distillation gave 2.15 g (68%) of a colorless oil; gc retention time 3.0 min.

UNH ir: 23489
Sadtler ir: 2887

Benzonitrile. To 0.025 mol of diphenylcadmium prepared in the usual way was added 3.0 g (0.025 mol) of phenyl cyanate in 25 mL of dry ether. Hydrolysis, work-up and Kugelrohr distillation gave 2.95 g (88%) of a colorless oil; retention time, 1.9 min.

UNH ir: 23494
Sadtler ir: 2255

RESULTS AND DISCUSSION

The usual methods for the formation of aromatic nitriles often require involved procedures. Because the Grignard reagent was used to advantage to produce aromatic nitriles, it was thought that the cadmium reagent might be as good, if not superior, for this synthetic preparation.

The Grignard procedures have been run at low temperatures, -78^{o} and -50^{o}, which are ideal conditions for tert-butyl and other unstable reagents. Another reason for the low temperatures was to reduce the amount of ketonic side product from a second addition of the Grignard reagent to the nitrile. The present report shows that good yields can be realized by using the organocadmium reagent at room temperature without concern for ketone formation. Although the yields in this report were not maximized, it is thought that higher yields could be achieved by using higher reaction temperatures (benzene solvent).

In another report, alkyl cyanates were used to prepare nitriles of the corresponding Grignard reagents. It was found that substitution to the hydrocarbon, to the extent of as much as 30%, was a serious side reaction. It would be of interest in subsequent research to compare the results of the cadmium reaction with alkyl cyanates with those of the Grignard reagent.

The cyano compounds of benzene, the isomeric toluenes and p-anisole were prepared in good yield as shown in Table XI. The proposed mechanism for this reaction is given in Scheme XVIII.

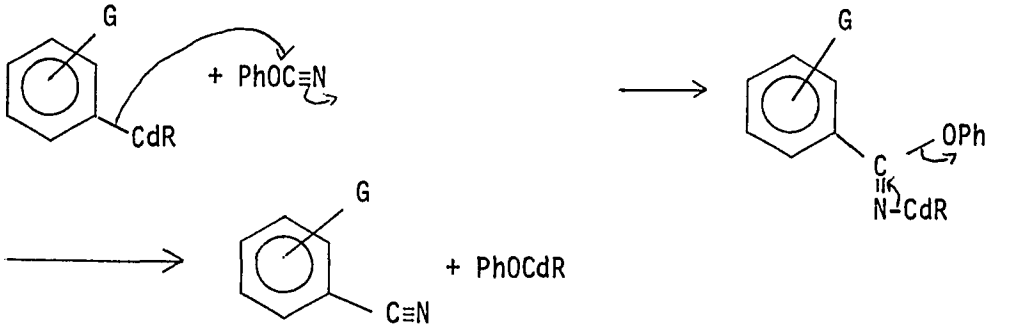
Another mechanism that involves a direct substitution of the aryloxy group by the cadmium substituent can be drawn for this reaction,

TABLE XI

The Reactions of Organocadmium Reagents with Aryl Cyanates

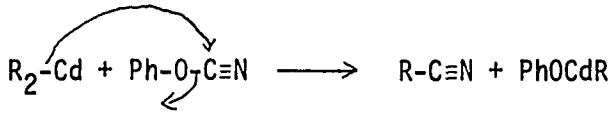
$$R_2Cd + R'OCN \longrightarrow RCN$$

R	R'	% Yield	bp of Nitrile (171)
Ph	Ph	88	69 (10 mm)
o-MePh	Ph	75	90 (15 mm)
m-MePh	Ph	73	84.5 (10 mm)
p-MePh	Ph	69	91 (11 mm)
p-MeOPh	1,4-Ph_2	40	mp 61-62



Scheme XVIII

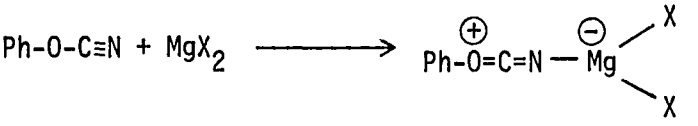
Scheme XIX. This may explain why, in the case of the Grignard reactions, no imido magnesium salt could be isolated.



Scheme XIX

It would be of interest to observe whether magnesium salts are necessary for the reaction to occur as shown in Scheme XX. This could be done

by purifying the organocadmium reagent and allowing it to react with phenyl cyanate.

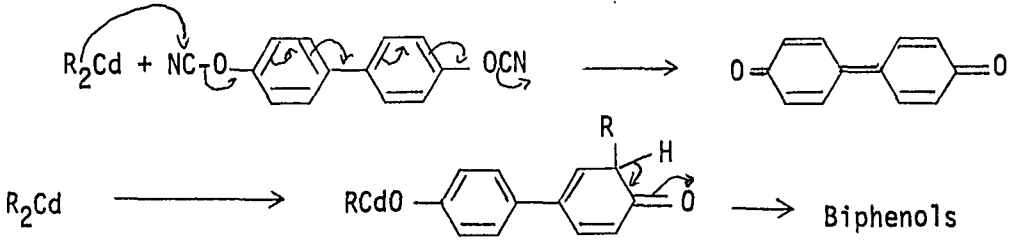


Scheme XX

It is interesting to notethat the yields of the phenyl cyanate reactions are greater than 50%. One of the products contains a cadmium-oxygen bond (RCdOPh), and these compounds are known (217) to react slowly a second time, if at all.

It should be mentioned here that, in the reaction of m-tolylcadmium with phenyl cyanate, no rearrangement products were observed by gc analysis. This is interesting in light of the fact that we showed that phenyl cyanate reacted with m-dianisylcadmium to give a 9% yield of rearranged para product (Part I).

The preparation of p-anisonitrile from the dicyanate of 4,4'-dihydroxybiphenyl proceeded in 40% yield, lower than that from reactions with phenyl cyanate. The former reagent has the advantage of being a solid and more stable;thus, it is easily handled and no special precautions are required. The low yields may be due to secondary reactions as shown in Scheme XXI. The by-product may not contain a cyanate and as a result may be reactive to organocadmium reagents.



Scheme XXI

In summary, whether one uses the Grignard reagent or the cadmium reagent, these routes to the nitriles could be the methods of choice since negligible side products are observed, and products are unambiguous and the yields are good to excellent. Furthermore, these procedures require much less elaborate manipulation than the usual methods.

C

INTRODUCTION

One of the most elusive functional groups in organic synthesis is the nitroso group. If sheer numbers of publications and reviews were an indication (218), one would think the route to the nitroso group was well-known and characterized. However, such is not the case. Because most syntheses of nitroso compounds are restricted by stringent reaction conditions, unavailability of starting materials, limitations on the scope of the reaction and low yields, a general procedure for a mild, efficient preparation of nitroso compounds is sorely needed.

HISTORICAL

Oxidations of primary aromatic amines by H_2SO_5 (219), peroxyacetic acid (220), and hydrogen peroxide in acetic acid (221) are the most common routes to aromatic nitroso compounds, although suppression of further oxidation is often a limiting factor to be considered.

Reductions of nitro compounds are likewise difficult to control at the nitroso stage (222), but often this is the method of choice, even though yields are low.

Free radical reactions of nitrosyl chloride with saturated hydrocarbons have been reported to result in good yields (223), but here the disadvantage is a lack of regioselectivity.

Ionic nitrosation requires active methylene compounds (224) with alkyl nitrites or nitrous acid under strongly basic or acidic conditions (225).

Classical nitrosation of aromatic compounds with nitrous acid is limited to highly activated aromatic rings such as phenols, naphthols, or secondary and tertiary anilines (Fischer-Hepp Reaction, Equation 58 (226)).

$$PhNR_2 + NaNO_2 + HCl \longrightarrow \underline{p}\text{-ON-Ph-}NR_2 \quad (80\text{-}89\%)$$

Equation 58

Pyrroles (227) and indoles (228) have been nitrosated by alkyl nitrites in the presence of metal alkoxides or by nitrous acid but here the position of attachment is totally controlled by the heterocyclic ring.

Other methods include the Baudisch oxidative nitrosation (229), the thermolysis of open-chain alkyl nitrites (230), addition of nitrosyl chloride to alkenes (231), nitrosative decarboxylation (232,233), and oxidation of hydroxylamines (234). Each of these suffers from one or more of the above mentioned limitations.

Recently organometallics have come under consideration as precursors for nitroso compounds. In 1970, it was reported that aromatic trimethyl stannanes are nitrosated with nitrosyl chloride. The yields of the corresponding aryl nitroso compounds ranged from poor for halogen substituted rings to moderate to good for highly activated rings (235). Polyalkylaryl- and activated arylmercury compounds have been nitrosated with nitrosyl chloride and nitrosyl sulfuric acid ($NOSO_4H$), respectively, with yields ranging from poor to moderate (236).

The most important synthesis to date of nitroso compounds from organometallics has been that involving the corresponding organothallium reagent (237). These reagents lead to excellent yields for the

polyalkylaryl substrates and to moderate yields for the benzene, anisole, and chlorobenzene substrates. This synthesis has seemingly great potential but suffers from the fact that thallium compounds are highly toxic.

Although there are early literature claims that Grignard reagents react with nitrosyl chloride to give nitrosobenzene in moderate yield, it has been shown in a recent investigation that, in fact, the nitrosobenzene was produced in only 3.2% yield (238). The Grignard reagent is believed to react further with the nitroso intermediate to produce symmetrically disubstituted amines (Equation 59). This reaction is

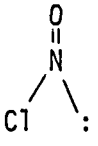
$$PhMgBr + NOCl \longrightarrow PhNO \xrightarrow{PhMgBr} Ph_2N\text{-}OMgBr \xrightarrow{PhMgBr}$$

$$Ph_2NMgBr + PhOMgBr \xrightarrow{H_2O} Ph_2NH + PhOH$$

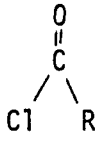
Equation 59

reminiscent of that of Grignard reagents with acid chlorides to give the corresponding alcohol.

Since nitrosyl chloride (CC) is isoelectronic with acid chlorides



CC



DD

(DD) it was proposed that the cadmium reagent, which adds only once to acid chlorides to produce ketones, would add only selectively to nitrosyl chloride to give nitroso compounds (Equation 60).

$$2RBr \xrightarrow{Mg/THF/N_2} 2RMgBr \xrightarrow{CdCl_2/THF/N_2} R_2Cd + 2MgBrCl$$

$$\xrightarrow{NOCl} 2R\text{-}NO + CdCl_2$$

Equation 60

The overall reaction then would be conversion of a halogen compound to a nitroso compound. The advantage of such a procedure would be the abundant availability of halogen compounds that can be utilized and the ability to direct the attachment.

EXPERIMENTAL

Nitrosyl chloride was prepared as described on page 125. All starting materials were either synthesized independently or were purchased from Aldrich Chemical Co. All temperatures are reported in degrees Centigrade.

The Reaction of Diphenylcadmium with Nitrosyl Chloride. To the phenyl Grignard reagent (0.04 mol) prepared in the usual manner, in THF, was added 3.7 g (0.2 mol) of cadmium chloride and the mixture was stirred for 30 min. To the mixture, cooled in an ice bath, was added dropwise a solution of 2.6 g (0.04 mol) of nitrosyl chloride in 25 mL of THF. The solution immediately took on a reddish color. After the addition the mixture was allowed to come to ambient temperature and then was poured onto crushed ice. Technical ether was added; the organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. Steam distillation of the residual brown oil resulted in the collection of first a green oil and then a yellow oil, both turning brown on standing. Column chromatography (silica or alumina) resulted in isolation of brown or yellow oils. Various separation and extraction techniques, including

UNH ir (green oil): 22332
Sadtler ir (PhNO): 21426

freeze drying, did not afford any solid product (PhNO mp: 67-68°). When the reaction was performed in ether or benzene similar results were obtained.

The Reaction of Di-p-Tolylcadmium with Nitrosyl Chloride. To the p-tolyl Grignard reagent (0.1 mol) in THF was added 11 g (0.05 mol) of cadmium chloride; after a reflux period of 30 min and cooling, 6.6 g (0.1 mol)

of nitrosyl chloride in 20 mL of THF was added dropwise. The mixture was stirred for 30 min at room temperature and then poured onto ice. Steam distillation gave a green oil, followed by a yellow oil; both turned brown on standing.

The Reaction of o-dianisylcadmium with Nitrosyl Chloride. To the Grignard reagent (0.1 mol) in THF was added 11 g (0.05 mol) of cadmium chloride, and the mixture was stirred for 30 min. A solution of 6.6 g (0.01 mol) of nitrosyl chloride in 25 mL of THF was added dropwise and stirring was continued for 30 min at room temperature. The mixture was then poured onto crushed ice and extracted with ether, which was dried (Na_2SO_4), concentrated in vacuo, and steam distilled to give only a yellow oil which quickly turned brown. On tlc analysis the crude product showed a band of green with high R_f.

The Reaction of Di-m-Trifluorophenylcadmium with Nitrosyl Chloride. To the Grignard reagent (0.05 mol) in THF was added with stirring 4.6 g (0.025 mol) of cadmium chloride. After the solution had been stirred for 30 min, 3.4g(0.05 mol) of nitrosyl chloride in 20 mL of THF was added dropwise, and stirring was continued for 30 min. The mixture was poured onto ice and extracted with ether; the ether layer was dried (Na_2SO_4) and concentrated in vacuo. Steam distillation gave only oils.

The Reaction of Di-p-Chlorophenylcadmium with Nitrosyl Chloride. To the Grignard reagent prepared from p-chlorobromobenzene, (0.05 mol) in THF, was added 4.6 g (0.025 mol) of cadmium chloride and the mixture was stirred for 30 min. A solution of 3.4 g (0.05 mol) of nitrosyl chloride in 39 mL of THF was added dropwise. After the usual work-up, as above, steam distillation produced only yellow and brown oils.

The Reaction of Diphenylcadmium with Nitrosobenzene. To a mixture of diphenylcadmium (0.05 mol) in ether was added a solution of 5.1 g of nitrosobenzene in ether. The reaction mixture immediately turned brown. After the addition and stirring for 30 min longer, the mixture was hydrolyzed in the flask with 25 mL of 15% HCl. The ether layer was separated, dried ($MgSO_4$) and concentrated in vacuo. Vacuum distillation produced a green oil (unchanged starting material). When the residue was subject to column chromatography (silica), five fractions were collected. The first fraction was a semisolid, which has the tlc characteristics and spectral properties of diphenylamine. The other fractions could not be identified. From the acid layer, after neutralization and ether extraction was obtained aniline (10%), identified by its ir and nmr spectra.

UNH ir:	23492
Sadtler ir:	3695
UNH nmr:	7796
Sadtler nmr:	191

RESULTS AND DISCUSSION

From the controlled experiment it appears that nitroso compounds do not survive treatment under the reaction conditions with organocadmium reagents. In fact this organometallic reacts with nitrosobenzene to give mixtures of products ranging from aniline to diphenylanime and probably various intermediate that could not be isolated. This is not surprising in light of the fact that the Grignard reagent reacts similarly with nitrosyl chloride to produce symmetrically disubstituted amines. It is interesting to speculate that perhaps if these reactions were carried out in the absence of magnesium salts, then perhaps serious side products might not result. It is known that in the absence of magnesium salts the organocadmium reagent is not as reactive with carbonyl compounds as when these salts are present. Although it had been found that inverse addition of the Grignard reagent to the nitrosyl chloride did not alter the product outcome, perhaps this would not be the case with the organocadmium reagents.

No solid compounds could be isolated from the reactions of organocadmium reagents with nitrosyl chloride. C-Nitroso compounds are known to be low-melting solids that are blue-green in color. Changing solvents did not seem to affect the reaction products. The instability of the nitrosobenzene formed (identified by comparison of its ir to that of Sadtler) was noted since, almost as soon as it was isolated, it turned yellow, then brown. Although much effort was devoted to obtaining the green nitroso compounds, little attention was paid to side products.

Perhaps interesting compounds were produced from the product mixtures that could be identified in the future.

BIBLIOGRAPHY

1. L. H. Klemm, R. Mann and C. D. Lind, J. Org. Chem., 23, 349 (1958).

2. W. G. Dauben and J. W. Collette, J. Amer. Chem. Soc., 81, 968 (1959).

3. R. H. Martin and J. Walravens, Bull. Soc. Chim. Belges, 69, 165 (1960).

4. D. A. Shirley, "Organic Reactions", Vol. 8, John Wiley and Sons, New York, N. Y., 1954, p 28.

5. J. Cason, Chem. Rev., 40, 15 (1947).

6. N. I. Sheverdina and K. A. Kocheshkov, "Methods of Elemento-Organic Chemistry", Vol. 3, North-Holland Pub. Co., Amsterdam, 1967, p 164.

7. N. O. V. Sonntag, Chem. Rev., 52, 237 (1953).

8. M. Cois and A. Mandelbaum, "The Chemistry of the Carbonyl Group", S. Patai Ed., London, Interscience Pub., 1966, p 303.

9. H. Gilman and F. Schulze, J. Amer. Chem. Soc., 47, 2002 (1925).

10. P. Sartori and H. J. Frohn, Chem. Ber., 107, 1195 (1974).

11. J. Chenault and F. Tatibouet, C. R. Acad. Sci., Paris, Ser. C, 262, 499 (1966); 264, 213 (1967).

12. J. O. Murdock and K. J. Klabunde, J. Org. Chem., 41, 1076 (1976).

13. Dr. R. D. Rieke, University of Nebraska, private communication.

14. D. V. Nightingale and L. D. Wadsworth, J. Amer. Chem. Soc., 67, 416 (1945).

15. O. G. Vashina and L. I. Vereshchagin, Zh. Org. Khim., 4, 2104 (1968); Chem. Abstr., 70, 67812e (1969).

16. M. Pailer and H. Gutwillinger, Monatsh. Chem., 108, 653 (1977).

17. E. Brown, E. Guilmet and J. Touet, Tetrahedron, 29, 2589 (1973).

18. J. Cason and F. S. Prout, J. Amer. Chem. Soc., 66, 47 (1944).

19. M. Langlais, A. Buzas, G. Soussan and P. Freon, C. R. Acad. Sci., Paris, Ser. C, 261, 2920 (1965).

20. R. R. Reinhard and J. A. Dixon, J. Org. Chem., 30, 1450 (1965).

21. J. Brunet, D. Paquer and P. Rioult, C. R. Acad. Sci., Paris, Ser. C, 277, 323 (1973).

22. K.-H. Schweer and A. Schwarz, Chem. Ber., 95, 620 (1962).

23. K. W. Bentley and D. G. Hardy, J. Amer. Chem. Soc., 89, 3267 (1967).

24. A. G. Viehe and M. Reinstein, Chem. Ber., 95, 2557 (1962).

25. E. Henry-Basch, J. Deniau, G. Emptoz, F. Huet, B. Marx and J. Michel, C. R. Acad. Sci., Paris, Ser. C, 262, 598 (1966).

26. F. Huet, J. Michel, C. Bernardon and E. Henry-Basch, C. R. Acad. Sci., Paris, Ser. C, 262, 1328 (1966).

27. G. Soussan and P. Freon, C. R. Acad. Sci., Paris, Ser. C,271, 211 (1970).

28. J. Michel and E. Henry-Basch, C. R. Acad. Sci., Paris, Ser. C, 262, 1387 (1966).

29. J. Kollonitsch, J. Chem. Soc., A, 456 (1966).

30. G. Soussan and P. Freon, C. R. Acad. Sci., Paris, Ser. C, 271, 211 (1970).

31. L. LeGuilly and F. Tatibouet, C. R. Acad. Sci., Paris, Ser. C, 262, 217 (1966).

32. K. W. Kraus, R. T. Bogan and R. M. Weier, Proc. Iowa Acad. Sci., 71, 205 (1964); Chem. Abstr., 63, 18138f (1965).

33. J. R. Sanders and E. C. Ashby, J. Organometal. Chem., 25, 277 (1970).

34. A. J. M. Reuvers, A. Sinnema, F. van Rantwijk, J. D. Remijnse and H. van Bekkum, Tetrahedron, 25, 4455 (1969).

35. K. Dimroth, A. Berndt and R. Vocland, Chem. Ber., 99, 3040 (1966).

36. D. Kurath, F. M. Ganis and M. Radakowich, Helv. Chim. Acta, 40, 933 (1957).

37. J. Cason, J. Amer. Chem. Soc., 68, 2078 (1946).

38. T. S. Muraski and C. Djerssi, J. Org. Chem., 33, 2962 (1968).

39. J. S. Brooks and G. A. Morrison, J. Chem. Soc, Perkin I, 2114 (1974).

40. R. E. Leslie and H. R. Henze, J. Amer. Chem. Soc., 71, 3480 (1949).

41. J. Cason and F. J. Schmitz, J. Org. Chem., 25, 1293 (1960).

42. D. V. Nightingale, W. S. Wagner and R. H. Wise, J. Amer. Chem. Soc., 75, 4701 (1953).

43. R. A. LeMahiew, J. Org. Chem., 32, 4149 (1967).

44. R. Heilman, G. de Gaudemaris and R. Heindl, C. R. Acad. Sci., Paris, Ser. C, 235, 544 (1952).

45. N. B. Chapman, K. Clarke and D. J. Harvey, J. Chem. Soc., C, 1202 (1971).

46. R. N. Renaud, D. Kovachic and L. C. Leitch, Can. J. Chem., 39, 21 (1961).

47. N. B. Chapman, K. Clarke, R. M. Pinder and S. N. Sawhaney, J. Chem. Soc., C, 293 (1967).

48. F. G. Bordwell and H. Schlechter, J. Amer. Chem. Soc., 89, 5868 (1967).

49. W. G. Dauben and K. A. Seagebarth, J. Amer. Chem. Soc., 73, 1853 (1951).

50. S. E. Cremer and D. S. Tarbell, J. Org. Chem., 26, 3653 (1961).

51. F. Fringvelli, V. Mancini and A. Titicchi, Tetrahedron, 25, 4249 (1969).

52. G. L. B. Carlson, F. H. Quina, B. M. Zarnegar and D. G. Whittey, J. Amer. Chem. Soc., 97, 347 (1975).

53. H. E. Zimmerman and R. D. McKelvey, J. Amer. Chem. Soc., 93, 3638 (1971).

54. R. Haller and H. J. Schneider, Chem. Ber., 106, 1312 (1973).

55. C. A. Bueler, H. A. Smith, K. V. Nayak and T. A. Magee, J. Org. Chem., 26, 1573 (1963).

56. K. W. Schweer, Atompraxis, 12, 85 (1966); Chem. Abstr., 65, 8802e (1966).

57. N. C. Deno and J. O. Turner, J. Org. Chem., 31, 1969 (1966).

58. K. Stockel, W. Stockel and T. Reichstein, Helv. Chim. Acta, 52, 1461 (1969).

59. C. Bernardon, E. Henry-Basch and P. Freon, C. R. Acad. Sci., Paris, Ser. C, 266, 1502 (1968).

60. G. Saucy, W. Koch, M. Muller and A. Furst, Helv. Chim. Acta, 53, 964 (1970).

61. K. B. Sharpless and K. M. Gordon, J. Amer. Chem. Soc., 76, 300 (1954).

62. L. J. Sargent, J. Org. Chem., 26, 1754 (1961).

63. R. Heilman and G. DeGaudemaris, C. R. Acad. Sci., Paris, Ser. C, 233, 874 (1951).

64. M. Renson and R. Huls, Bull. Soc. Chim. Belges, 61, 599 (1952).

65. A. P. Kurtz and C. R. Dawson, J. Med. Chem., 14, 734 (1971).

66. E. V. Heyningen, C. N. Brown, F. Jose, J. K. Henderson and P. Stark, J. Med. Chem., 9, 675 (1966).

67. J. M. Watson, J. L. Irvine and R. M. Roberts, J. Amer. Chem. Soc., 95, 3348 (1973).

68. L. M. Jackman, J. A. Mills and J. S. Shannon, J. Amer. Chem. Soc., 72, 4814 (1950).

69. E. Brown, J. Lavoue and R. Daal, Tetrahedron, 29, 455 (1973).

70. R. E. Leslie and H. R. Henze, J. Amer. Chem. Soc., 71, 3482 (1949).

71. L. H. Klemm and T. Largman, J. Amer. Chem. Soc., 76, 1608 (1954).

72. J. K. Stille and R. A. Newsom, J. Org. Chem., 26, 1375 (1961).

73. E. Buchte and H. Maar, Ann. Chem., 674, 129 (1964).

74. R. D. Bush, C. M. Gozino, G. D. Homer and C. H. Sommer, J. Organomet. Chem., 80, 37 (1974).

75. M. J. Ashton, A. S. Bailey and E. R. H. Jones, J. Chem. Soc., Perkin I, 1665 (1974).

76. R. C. Elderfield and V. B. Meyer, J. Amer. Chem. Soc., 76, 1883 (1954).

77. S. D. Wyrick, I. H. Hall, C. P. Piantadosi and C. R. Fenske, J. Med. Chem., 19, 219 (1976).

78. S. Iwaki, S. Marumo, T. Saito, M. Yamada and K. Katagiri, J. Amer. Chem. Soc., 96, 7842 (1974).

79. M. Renson and J. Bonhomme, Bull. Soc. Chim. Belges, 68, 667 (1959).

80. J. Kollonitsch, J. Chem. Soc., A, 453 (1966).

81. M. Renson and J. Bonhomme, Bull. Soc. Chim. Belges, 68, 437 (1959).

82. M. Renson and J. Beetz, Bull. Soc. Chim. Belges, 70, 537 (1961).

83. J. Cason and E. J. Reist, J. Org. Chem., 23, 1668 (1958).

84. J. Cason and E. J. Reist, J. Org. Chem., 23, 1675 (1958).

85. G. Soussan and P. Freon, C. R. Acad. Sci., Paris, Ser. C, 262, 933 (1966).

86. G. Soussan and P. Freon, Bull. Soc. Chim. Fr., 4228, 4233 (1972).

87. G. D. Gutsche and J. W. Baum, J. Amer. Chem. Soc., 90, 5862 (1968).

88. T. S. Cantrell and H. Schechter, J. Amer. Chem. Soc., 89, 5868 (1967).

89. F. Tatibouet and P. Freon, C. R. Acad. Sci., Paris, Ser. C, 240, 1231 (1955).

90. T. Negi, et al, Bull. Chem. Soc. Japan, 47, 2398 (1974).

91. E. K. Euranto and L. Puuppomen, Acta Chim. Scand., 24, 363 (1970).

92. F. Tatibouet and P. Freon, Bull. Chem. Soc. Fr., 1496 (1963).

93. M. D. Soffer, N. S. Strauss, M. D. Trail and K. W. Sherk, J. Amer. Chem. Soc., 69, 1684 (1947).

94. R. Golse and A. Liermain, C. R. Acad. Sci., Paris, Ser. C, 252, 3076 (1956).

95. G. W. Stacy and R. M. McCurdy, J. Amer. Chem. Soc., 76, 1944 (1954).

96. P. Freon and F. Tatibouet, C. R. Acad. Sci., Paris, Ser. C, 244, 2399 (1957).

97. E. von Rudloff, Can. J. Chem., 36, 486 (1958).

98. R. Huisgen and E. Ravenbusch, Ann. Chem., 641, 51 (1961).

99. J. G. Cannon, Y. Lin and J. P. Long, J. Med. Chem., 16, 27 (1973).

100. J. M. Simson and W. Lwowski, J. Amer. Chem. Soc., 91, 5107 (1969).

101. M. Kinoshita, K. Ishii and S. Umetawa, Bull. Chem. Soc. Japan, 44, 3395 (1971).

102. K. M. Patel, H. J. Pownall, J. D. Morrisett and J. T. Sparrow, Tetrahedron Lett., 4015 (1976).

103. A. Kuldvere and N. Lofgren, Acta Chim. Scand., 21, 2363 (1967).

104. R. N. Chakravarti and N. Dutta, Ind. J. Chem., 51, 239 (1974).

105. S. Swaminatham and M. S. Newman, Tetrahedron, 2, 88 (1958).

106. R. F. Taylor, J. Chem. Soc., 1106 (1947).

107. J. Cason and F. J. Schmitz, J. Org. Chem., 28, 552 (1963).

108. E. Leete and J. O. Olsen, J. Amer. Chem. Soc., 94, 5472 (1972).

109. J. Cason and F. J. Schmitz, J. Org. Chem., 28, 555 (1963).

110. C. K. Warren and B. C. L. Weedon, J. Chem. Soc., 3972 (1958).

111. C. K. Warren and B. C. L. Weedon, J. Chem. Soc., 3986 (1958).

112. S. Akiya and Y. Nakazawa, J. Pharm. Soc. Japan, 76, 1401 (1956); Chem. Abstr., 51, 5608d (1957).

113. N. L. Allinger and E. S. Jones, J. Org. Chem., 27, 70 (1962).

114. W. L. Hubbell and H. M. McConnell, J. Amer. Chem. Soc., 93, 314 (1971).

115. V. R. Mamdapur, P. P. Pai, K. K. Chakravarti, U. G. Nayak and S. C. Bhattacharyya, Tetrahedron, 20, 2601 (1964).

116. D. Cobern, J. S. Hobbs, R, A. Lucas and D. J. Mackenzie, J. Chem. Soc. C, 1897 (1966).

117. R. N. McDonald and G. E. Davis, J. Org. Chem., 34, 1916 (1969).

118. J. Kenyon and D. P. Young, J. Chem. Soc., 263 (1941).

119. K. Mislow and J. Brenner, J. Amer. Chem. Soc., 75, 2318 (1953).

120, G. Uhde and G. Ohnloff, Helv. Chim. Acta, 56, 2548 (1973).

121. G. Stork and R. Breslow, J. Amer. Chem. Soc., 75, 3292 (1953).

122. D. J. Collins and J. J. Hobbs, Aust. J. Chem., 27, 1753 (1974).

123. S. Masamune, J. Amer. Chem. Soc., 86, 291 (1964).

124. K. W. Bentley and D. G. Hardy, J. Amer. Chem. Soc., 89, 3267 (1967).

125. M. Harispe, D. Mea and A. Horeau, Bull. Soc. Chim. Fr., 1035 (1964).

126. K. B. Wiberg, B. R. Lowry and T. H. Colby, J. Amer.Chem. Soc., 83, 3998 (1961).

127. D. J. Cram and F. L. Harris, J. Amer. Chem. Soc., 89, 4642 (1967).

128. R. A. Cormier, W. L. Schreiber and W. G. Agosta, J. Amer. Chem. Soc., 95, 4873 (1973).

129. J. W. Wilt, C. J. Parsons, C. A. Schneider, D. G. Schultenover and W. J. Wagner, J. Org. Chem., 33, 694 (1968).

130. L. E. Friedrich and R. A. Cormier, J. Org. Chem., 36, 3011 (1971).

131. I. Heilbron, E. R. H. Jones and D. G. O'Sullivan, J. Chem. Soc., 866 (1946).

132. A. Berger and T. G. Selin, US Patent 3,845,127, 29 Oct. 1974; Chem. Abstr., 82, P86401 (1975).

133. A. Deflandre, A. Lheureux, A. Rioual and J. Lemaire, Can. J. Chem., 54, 2127 (1976).

134. P. J. Wagner and G. S. Hammond, J. Amer. Chem. Soc., 88, 1245 (1956).

135. B. Riegel and F. S. Prout, J. Org. Chem., 13, 933 (1948).

136. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, J. Amer. Chem. Soc., 74, 4223 (1952).

137. W. Cole and P. L. Julian, J. Amer. Chem. Soc., 67, 1369 (1945).

138. R. W. Kierstead and A. Faraone, J. Org. Chem., 32, 704 (1967).

139. F. B. Hirschmann and H. Hirschmann, J. Org. Chem., 38, 1270 (1973).

140. P. L. de Benneville, J. Org. Chem., 6, 462 (1941).

141. C. H. Wang, R. Isensee, A. M. Griffith and B. E. Christensen, J. Amer. Chem. Soc., 69, 1909 (1947).

142. D. V. Nightingale and J. A. Gallagher, J. Org. Chem., 24, 501 (1959).

143. J. Tirouflet, Bull. Soc. Chim., Bretagne, 26, 69 (1951); Chem. Abstr., 47, 8694 (1953).

144. J. Tirouflet, Bull. Soc. Chim., Bretagne, 26, 81 (1951);Chem. Abstr., 47, 8695 (1953).

145. D. S. Tarbell and J. R. Price, J. Org. Chem., 21, 144 (1956); 22, 245 (1957).

146. J. Cason and F. S. Prout, J. Amer. Chem. Soc., 66, 46 (1944).

147. D. Abenhaim and E. Henry-Basch, C. R. Acad. Sci., Paris, Ser. C, 267, 87 (1968); D. Abenhaim, E. Henry-Basch and P. Freon, Bull. Soc. Chim, Fr., 4043 (1969).

148. C. Agami, M. Andrec-Taussig and C. Prevost, Bull. Soc. Chem. Fr., 2596 (1966).

149. K. H. Thiele, J. Koehler and P. Zdunneck, Z. Chem., 7, 307 (1967).

150. P. R. Jones, P. D. Sherman and K. Schwarzenberg, J. Organomet. Chem., 10, 521 (1967).

151. "Sadtler Standard Spectra", Sadtler Laboratories, Philadelphia, PA.

152. J. R. Johnson and C. G. Gauerke, "Organic Synthesis", Coll. Vol. I, J. Wiley, New York, NY, p 123.

153. J. W. Bruhl, Z. physik. Chem., 22,379 (1897).

154. D. W. Speekman and J. P. Wibault, Rec. Trav. Chim. Pays-Bas, 61, 383 (1942).

155. D. W. Mathieson and G. Newberry, J. Chem. Soc., 1133 (1949).

156. W. A. Sheppard, "Organic Synthesis", Coll. Vol. V, J. Wiley, New York, NY, p 1085.

157. W. G. Brown, A. H. Widiger and N. J. Letang, J. Amer. Chem. Soc., 61, 2597 (1939).

158. D. J. Flood, "Organic Synthesis", Coll. Vol. II, J. Wiley, New York, NY, p 295.

159. J. H. Simons and E. O. Ramler, J. Amer. Chem. Soc., 65, 391 (1943).

160. D. S. Tarbell and D. K. Fukushima, "Organic Synthesis", Coll. Vol. III, J. Wiley, New York, NY, p 809.

161. F. G. Bordwell and H. M. Anderson, J. Amer. Chem. Soc., 75, 6021 (1953).

162. G. Schwartz and W. Kohlhaus, Chem. Ber., 39, 3343 (1906).

163. E. Grigat and R. Putter, Chem. Ber., 97, 3012 (1964).

164. W. A. Bonner, J. Amer. Chem. Soc., 72, 4270 (1950).

165. S. C. Watson and J. F. Eactham, J. Organometal. Chem., 9, 165 (1967).

166. H. Gilman and L. L. Heck, J. Amer. Chem. Soc., 52, 4949 (1930).

167. E. Bergmann and A. Bondi, Chem. Ber., 64B, 1455 (1931).

168. O. L. Brady and J. N. E. Day, J. Chem. Soc., 114 (1934).

169. K. Fukui, H. Kitano, T. Osaka, Y. Inamoto and H. Shirai, Nippon Kagaku Zasshi, 79, 1120 (1958); Chem. Abstr., 54, 5519c (1960).

170. W. J. Humphlett, M. J. Weiss and C. R. Hauser, J. Amer. Chem. Soc., 70, 4020 (1948).

171. "Handbook of Chemistry and Physics", The Chemical Rubber Company, 52nd Ed., Cleveland, Ohio, 1972.

172. R. T. Arnold and S. T. Kulenovic, Synth. Comm., 7, 223 (1977).

173. R. D. Reike and S. E. Bales, J. Amer. Chem. Soc., 96, 1775 (1974).

174. C. F. Lane, Aldrichemica Acta, 10, 141 (1977).

175. P. Grammaticakis, Bull. Soc. Chem. Fr., 93 (1953).

176. A. W. Hoffmann, Chem. Ber., 3, 275 (1870).

177. W. G. Davies and F. G. Mann, J. Chem. Soc., 276 (1944).

178. D. E. Pearson, D. Cowan and J. D. Beckler, J. Org. Chem., 24, 509 (1959).

179. C. D. Ritchie and W. F. Sager, "Prog. in Phys. Organic Chem.", Vol. 2, Intersci, Pub., New York, NY, p 323.

180. T.-L. Ho, Chem. Rev., 75, 1 (1975).

181. J. Cason, J. Org. Chem., 13, 227 (1948).

182. B. Oddo, Chem. Ber., 43, 1012 (1910).

183. S. J. Sylvia, University of New Hampshire, unpublished results.

184. For reviews see: a) R. A. Heacock and S. Kasparek, "Adv. in Hetero. Chem.", Vol 10, Acad. Pr., New York, NY, 1969, p 43; and b) J. C. Powers, "Heterocyclic Compounds: Indoles", W. J. Houlihan Ed. Vol II, J. Wiley, New York, NY, p 127.

185. S. Hishada, Nippon Nagaku Zasshi, 72, 312 (1951); Chem. Abstr., 46, 5038 (1952).

186. N. P. Buu-Hoi, E. Bisagni, R. Royer and C. Routier, J. Chem. Soc., 625 (1957).

187. C. D. Nenitzescu, Bull. Soc. Chim. Romania, 11, 130 (1930); Chem. Abstr., 24, 2458 (1930).

188. A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chem.", J. Wiley, New York, NY, p 174.

189. Ref. 184 A, p 109.

190. M. G. Reinecke, J. F. Sebastian and H. W. Johnson, J. Org. Chem., 36, 3091 (1971).

191. M. G. Reinecke, J. F. Sebastian, H. W. Johnson and C. Pyum, J. Org. Chem., 37, 3066 (1972).

192. Ref. 184 b, p 151.

193. N. Campbell and R. C. Cooper, J. Chem. Soc., 1208 (1935).

194. O. Schmitz-Dumont, K. Hamann and K. H. Geller, Ann. Chem., 504, 1 (1933).

195. P. Seidel, Chem. Ber., 77B, 797 (1944).

196. W. Madelung, Ann. Chem., 405, 58 (1914).

197. P. E. Verkade, J. Lieste and E. G. G. Warner, Rec. Trav. Chim. Pay-Bas, 64, 289 (1945).

198. W. E. Noland, L. R. Smith and K. R. Rush, J. Org. Chem.,30, 3457 (1965).

199. H. F. Hodgson and G. P. Smith, J. Chem. Soc., 3544 (1957).

200. E. Fischer and T. Schmitt, Chem. Ber., 21, 1071 (1888).

201. E. L. Brown and N. Campbell, J. Chem. Soc., 1699 (1937).

202. F. Brown and F. G. Mann, J. Chem. Soc., 847 (1948).

203. F. G. Mann and R. C. Haworth, J. Chem. Soc., 670 (1944).

204. Ref. 184 b, p 142.

205. J. Thomas, J. Organometal. Chem., 101, 249 (1975).

206. J. R. Morton and H. W. Wilcock, "Inorganic Synthesis", Vol IV, McGraw Hill, 1953, p 49.

207. W. A. Noyes, "Organic Synthesis", Coll. Vol. II, J. Wiley, New York, NY, p 108.

208. L. J. Dolby and R. M. Rodia, J. Org. Chem., 35, 1493 (1970).

209. E. van Hulle, "Methoden der Organischen Chemie", Houben Weyl, Vol 4, G. Thieme Verlag, Stutgart, Germany, 1954. p 613.

210. D. Martin and A. Weise, Chem. Ber., 100, 3736 (1967).

211. M. Hedayatullah, Bull. Soc. Chem. Fr., 1472 (1968); E. Grigat, Angew. Chem., Intern. Ed. Engl., 11, 949 (1972); E. Kuhle, Angew. Chem., Intern. Ed. Engl., 12, 630 (1973).

212. D. Martin, A. Weise, H.-J. Viclas and S. Rackow, Chem. Ber., 100, 3756 (1967).

213. D. Martin and S. Rackow, Chem. Ber., 98, 3662 (1965).

214. E. Grigat, R. Putter and E. Muhlbauer, Chem. Ber., 98, 3777 (1965).

215. A. Holm and E. Huge-Jensen, Acta Chem. Scand., 28B, 705 (1974).

216. E. Vowinkel and H.-J. Baese, Chem. Ber., 107, 1213 (1974).

217. P. R. Jones, E. J. Goller and W. J. Kaufmann, J. Org. Chem., 34, 3566 (1969).

218. a) R. Stroh, "Methoden der Organischen Chemie", Houben Weyl, Vol 10/1, G. Thieme Verlag, Stutgart, Germany, 1971, p 891; b) J. H. Boyer, "The Chemistry of the Nitro and Nitroso Groups", Intersci. Pub., New York, NY, 1970, p 215; c) P. A. S. Smith, "Open-chain Nitrogen Compounds," Vol. 2, Benjamin, New York, NY, 1966, p 355; d) L. J. Beckman, W. A. Fessler, and M. A. Kise, Chem. Rev., 48, 352 (1951).

219. F. B. Malloy, K. E. Schueller, and C. S. Wood, J. Org. Chem., 26, 3312 (1961).

220. H. Meister, Ann. Chem., 679, 83 (1964).

221. R. R. Holmes and R. D. Boyer, J. Amer. Chem. Soc., 82, 3454 (1960).

222. E. B. Dickinson, J. Amer. Chem. Soc., 86, 3580 (1964).

223. E. J. Burrell, Jr., J. Phys. Chem., 66, 401 (1962).

224. O. Touster, Org. Reactions, 7, J. Wiley, New York, NY, 327 (1953).

225. Y. Otsuji, Y. Tsujii, Y. Akihiko, and E. Imoto, Bull. Chem. Soc. Japan, 44, 219 (1971).

226. For a review see: P. D. D. de le Mare and J. H. Ridd, "Aromatic Substitution - Nitration and Halogenation", Academic Press, New York, NY, 1959, p 94.

227. E. T. Borrow, D. O. Holland, and J. Kenyon, J. Chem. Soc., 1075 (1946).

228. See Part II A of this thesis.

229. I. Tanimoto, Bull. Chem. Soc. Japan, 43, 139 (1970).

230. B. G. Gowanlock and J. Trotman, J. Chem. Soc., 1670 (1956).

231. M. M. Rogic, T. R. D. Emmin, R. Fuhrmann, and F. W. Koff, J. Amer. Chem. Soc., 97, 3241 (1975).

232. R. A. Henry, J. Org. Chem., 23, 648 (1958).

233. K. M. Ibne-Rasa, J. Amer. Chem. Soc., 84, 4962 (1962).

234. G. H. Coleman, C. M. McCloskey, and F. A. Stuart,"Organic Synthesis", Coll. Vol. III, J. Wiley, New York, NY, p 668.

235. E. H. Bartlett, C. Easborn, and D. R. M. Walton, J. Chem. Soc., C, 1717 (1970).

236. E. Yu. Belyaev, L. M. Gornstaev, and S. V. Petrova, Zh. Org. Khim., 11, 1931 (1975); Chem. Abstr., 84, 58817 (1976).

237. E. C. Taylor, R. H. Danforth, and A. McKillop, J. Org. Chem., 38, 2088 (1973).

238. W. I. Waters and P. G. Marsh, J. Org. Chem., 40, 3344, 3349 (1975).